Protocol Title:	A RANDOMIZED, CROSSOVER, DOUBLE BLIND, PLACEBO CONTROLLED, PHASE 2 STUDY TO EVALUATE THE EFFICACY AND SAFETY OF LORUNDROSTAT IN ADDITION TO SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS, IN ADULTS WITH HYPERTENSION AND CHRONIC KIDNEY DISEASE WITH ALBUMINURIA
Protocol Number:	MLS-101-206
Test Products:	Lorundrostat (MLS-101)
Study Phase:	2
IND Number:	167026
Study Sponsor:	Mineralys Therapeutics, Inc. 150 N. Radnor Chester Rd. – Suite F200 Radnor, PA 19087
SAE Reporting:	Email: safety@caidya.com Fax: +1-919-573-0332
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1. SYNOPSIS

Name of Sponsor/Company:

Mineralys Therapeutics, Inc.

Name of Test Products:

Lorundrostat (MLS-101): *N*-(*trans*-4-acetamidocyclohexyl)-2-{4-[5-(4-methylphenyl)-1,2,4-triazin-3-yl]piperazin-1-yl}acetamide

Name of Active Ingredients:

Lorundrostat

Brief Title of Study:

Efficacy and Safety of Lorundrostat in Addition to Sodium-Glucose Cotransporter-2 Inhibitors in Subjects with Hypertension and Chronic Kidney Disease with Albuminuria

Number of Study Center(s): Approximately 35-45 investigational centers in the United States (US)

Study Period:	**Phase of Development:**
First subject enrolled: Q1 2024 Estimated time of last subject last visit: Q1 2025	2

Objectives and Endpoints:

Primary Objective:

- To assess the effect of lorundrostat 25 mg once daily (QD), in addition to a sodium-glucose cotransporter-2 inhibitor (SGLT2i), on systolic blood pressure (SBP) in subjects with hypertension and chronic kidney disease (CKD) with albuminuria on stable treatment with an angiotensin converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB)

[redacted]

Safety Objective

- To investigate the safety and tolerability of lorundrostat, in addition to a SGLT2i, in subjects with hypertension and CKD with albuminuria on stable treatment with an ACEi/ARB

[redacted]

Endpoints:

Primary Endpoint:

- Placebo-adjusted change from baseline in automated office blood pressure (AOBP) SBP at Study Week 4

[redacted]

Safety Endpoints:

- Incidence and severity of adverse events (AEs)
- Clinically significant changes in vital signs (body temperature, heart rate, and respiratory rate), physical examination and electrocardiogram (ECG) parameters
- Clinically significant changes in clinical laboratory assessments (hematology, chemistry, and urinalysis)
- Incidence of AEs of Special Interest (AESI)
    - Modification of study drug dose due to hyperkalemia (e.g., dose reduction, dose hold, or permanent dose discontinuation)
    - Modification of study drug dose due to hyponatremia (e.g., dose reduction, dose hold, or permanent dose discontinuation)
    - Hypotension with symptoms (e.g., light-headedness, dizziness, presyncope, or syncope)
    - Severely elevated blood pressure (BP; AOBP SBP >180 mmHg or AOBP DBP >110 mmHg)
    - Modification of study drug dose due to hypercortisolism (morning serum cortisol >35 µg/dL, confirmed by 24-hour urinary free cortisol)
    - Discontinuation of study drug due to hypocortisolism confirmed by adrenocorticotropic hormone (ACTH; Cosyntropin) stimulation test
    - Overdose of study drug
    - Modification of study drug dose due to reduction in kidney function (e.g., dose reduction, dose hold, or permanent dose discontinuation)

[redacted]

Methodology:

This is a randomized, double-blind (DB), placebo controlled, crossover study with a two-period, two-sequence (2x2) design evaluating the efficacy and safety of 25 mg QD lorundrostat (an aldosterone synthase inhibitor [ASI]) in addition to a SGLT2i for the treatment of hypertension in subjects with CKD and albuminuria despite receiving stable treatment with an ACEi or an ARB. Subjects will be at least 18 years old with hypertension, and mild to severe CKD with albuminuria at the Screening Visit. The study consists of a 2-week screening period, a 2-week run-in period where subjects will either begin study provided dapagliflozin 10 mg or continue on their regularly prescribed SGLT2i, and two DB 4-week treatment periods separated by a 4-week washout period (Figure 1). Subjects will be randomized (1:1) to two treatment sequences: lorundrostat-placebo (LP) and placebo-lorundrostat (PL).

Treatment allocation will be organized as follows:

- Treatment Period 1 (DB Study Week 0 to Study Week 4): Subjects will receive a lorundrostat 25 mg (sequence LP) or one matching lorundrostat-placebo tablet (sequence PL) dosed orally QD.
- Washout (Study Week 4 to Study Week 8): All subjects will receive matching placebo dosed orally QD.
- Treatment Period 2 (DB Study Week 0 to Study Week 4): Subjects will receive one matching lorundrostat-placebo tablet (sequence LP) or a lorundrostat 25 mg (sequence PL) dosed orally QD.

During the DB and Washout periods, subjects will continue their background therapy including ACEi/ARB and SGLT2i.

Following the completion of the study, subjects will be offered the opportunity to participate in a separate open label extension (OLE) study. If subjects do not enter the OLE, a final End-of-Study (EoS) safety visit will take place 2 weeks after the last dose of study drug.

Number of Subjects (planned): Approximately 60 subjects

Eligibility Criteria:

Subjects not meeting all inclusion criteria, or meeting at least one exclusion criterion, may be re-screened if there is a reasonable probability of reversal. Retesting of laboratory samples, and a repeat AOBP assessment is allowed in the event of technical failure. Inclusion in the study of any subject who meets all eligibility criteria on rescreening will be at the discretion of the Investigator.

Inclusion Criteria:

Subjects eligible for inclusion in this study must meet **all** the following criteria:

1. Written informed consent, obtained before any study-related assessment is performed
2. At least 18 years of age at the time of signing the informed consent form (ICF)
3. At Screening, UACR of 200-5000 mg/g, inclusive, in first morning urine void
4. At Screening, eGFR of ≥30 mL/min/1.73 m^2
5. At Screening, AOBP SBP of 135-180 mmHg, inclusive
6. At Randomization, AOBP SBP of 135-180 mmHg, inclusive
7. On a stable treatment with an ACEi or ARB for at least 4 weeks prior to Screening
8. At Screening, serum cortisol (morning measurement, blood draw as close to 8 AM as possible between 3 and 22 µg/dL, inclusive)
9. At Screening, body mass index (BMI) of ≥18 kg/m^2

10. Fertile male subjects and female subjects of childbearing potential must agree to use an acceptable method of contraception from the Screening Visit to 28 days after the last dose of study drug in each study part
11. Willing and able to comply with the study instructions and attend all scheduled study visits, and are capable of providing informed consent

Exclusion criteria:

Subjects meeting any of the following criteria are **not** eligible for inclusion in this study:

1. Women who are pregnant, plan to become pregnant, or are breast-feeding
2. Subjects with known hypersensitivity to lorundrostat or any of its respective excipients
3. Subjects with known hypersensitivity to dapagliflozin or any of its respective excipients (subjects beginning dapagliflozin only)
4. Treatment, or anticipated treatment, with any prohibited medication within the timeframes described in Section 6.9 of this protocol.
5. Treatment, or anticipated treatment, with triamterene and amiloride
6. Participation in a trial involving an investigational device or drug within 4 weeks or 5 half-lives (whichever is longer) prior to the Screening Visit
7. Previous treatment with lorundrostat or other ASI within 4 weeks or 5 half-lives (whichever is longer) prior to the Screening Visit
8. At Screening, serum potassium >5.0 mmol/L
9. At Randomization, serum potassium >5.0 mmol/L (prior to first dosing of study drug)
10. At Screening, serum sodium <135 mmol/L (corrected for hyperglycemia using the Katz formula). Rescreening of subjects with an exclusionary serum sodium is only allowed if two consecutive measurements at least one week apart are ≥135 mmol/L
11. Total bilirubin >2x upper limit of normal (ULN) except for those with a diagnosis of Gilbert's syndrome, unless approved by the Medical Monitor
12. History of clinically significant hyponatremia within 1 year prior to Screening
13. History of adrenal insufficiency or an abnormal ACTH stimulation test within 1 year prior to Screening
14. Hospitalization for the treatment of urgent or emergent hypertension within 1 year prior to Screening
15. Current, known or presumed white coat hypertension/significant white coat effect (as defined in the study reference manual [SRM])
16. Current, known or presumed orthostatic hypotension
17. Current, known or presumed autonomic dysfunction
18. Arm circumference >55 centimeters at Screening
19. Subjects with a previously proven secondary cause of hypertension are excluded with the following exceptions:
    a. Subjects with documented sleep apnea are eligible to participate
    b. Subjects with documented primary hyperaldosteronism are eligible to participate if they discontinue use of a mineralocorticoid receptor antagonist (MRA). They should have <20 mmHg increase in AOBP SBP, and AOBP SBP <150 mmHg at Randomization. MRA treatment may be tapered over a one-week period.

20. Use of epithelial sodium channel (ENaC) inhibitors or MRAs, including, but not limited to amiloride, triamterene, spironolactone, eplerenone, finerenone, from 4 weeks prior to the Screening Visit and during study participation. With the exception of MRAs in primary aldosteronism.
21. Medical history of kidney disease related to autoimmune diseases (lupus, anti-neutrophil cytoplasmic antibody [ANCA] vasculitis), multiple myeloma or other known paraproteins, infiltrative diseases of the kidney, obstructive nephropathy, cystic kidney diseases, and renal transplantation
22. Medical history of advanced liver disease, including cirrhosis
23. Medical history of active autoimmune disease or recent (within 30 days) or anticipated need for immunosuppressive therapy
24. Subjects with a medical history of urosepsis and pyelonephritis, lower limb amputation, genital mycotic infections, necrotizing fasciitis of the perineum (Fournier's Gangrene)
25. History of heart failure, myocardial infarction, stroke, or transient ischemic attack within 6 months prior to Screening. Heart failure of New York Heart Association (NYHA) Class II or more requires approval by the Medical Monitor
26. Diabetes mellitus with a glycosylated hemoglobin (HbA_{1c}) >10% (>86 mmol/mol) at Screening
27. Diabetes mellitus with >1 severe hypoglycemic event or severe diabetic ketoacidosis event (events requiring external help) in the 12 months prior to Screening, or with a history of impaired hypoglycemia awareness at Screening
28. Planned major surgery requiring hospitalization during the study period or performed within 4 weeks prior to the Screening Visit
29. History of malignant neoplasms within the 5 years prior to Screening except for known history of basal and squamous cell skin cancer and any carcinoma *in-situ*
30. Known or suspected abuse of illicit drugs or alcohol within 1 year prior to the Screening Visit
31. In the opinion of the Principal Investigator (PI), any other condition that will preclude participation in the study

Test Products, Dosage, and Mode of Administration:

Lorundrostat will be provided in 12.5 mg, and 25 mg tablets (equivalent to 14.74 mg, and 29.48 mg of lorundrostat monohydrobormide [HBr]). The daily dose of lorundrostat will not exceed 25 mg.

Lorundrostat: 25 mg tablets taken orally QD at approximately the same time each morning for 4 weeks.

Reference Product, Dosage and Mode of Administration:

Lorundrostat-placebo: Tablet matching the appearance of lorundrostat but without active substance, administered analogously to lorundrostat.

Duration of Subject's Participation Including Follow-up:

The expected duration of the study for each subject from Screening to the End of Study visit is expected to be:

Approximately 18 weeks

Statistical Methods:

Analysis Sets

The intent-to-treat (ITT) analysis set includes all subjects, regardless of whether treatment was received.

The full analysis set (FAS) will include all subjects who receive at least one dose of study drug. Subjects will be categorized according to the treatment assignment.

The safety analysis set (SAF) will include all subjects who receive at least one dose of study drug. Subjects will be categorized according to the treatment received in the respective study periods.

The population pharmacokinetics (popPK) analysis set will include all subjects who received at least one dose of lorundrostat and had at least one evaluable popPK sample taken. Subjects in this analysis set will be categorized according to the treatment received.

Sample Size

Approximately 60 subjects randomized in a 1:1 ratio to the two sequences (LP and PL) will provide 85% power to detect a placebo-adjusted change in AOBP SBP of at least 5.5 mmHg, assuming a 14 mmHg as a standard deviation of change, and 1-sided alpha of 0.05.

Statistical Analyses

Unless otherwise specified, demographic and baseline characteristics will be summarized for the ITT analysis set. Efficacy outcomes will be analyzed using the FAS, unless otherwise specified. Safety outcome analyses will be performed on the SAF.

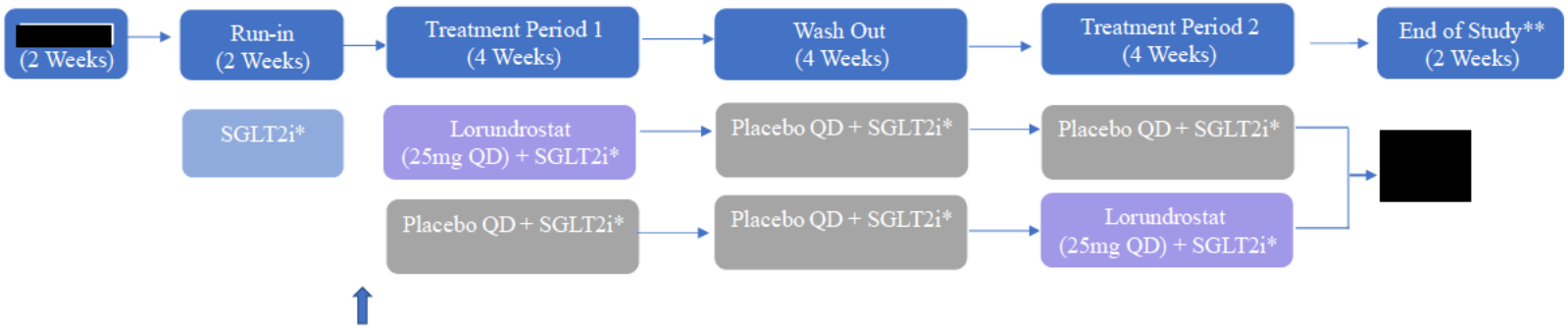
For continuous variables, the descriptive statistics of n, mean, standard deviation, median, 25th percentile, 75th percentile, minimum, and maximum will be summarized. The frequency and percentage of observed levels will be reported for all categorical variables.

The primary analysis of the primary efficacy estimand will assess the superiority of lorundrostat treatment compared to placebo in change from baseline in AOBP SBP at Study Week 4. Each subject contributes two pairs of treatment observations (change at Study Week 4 from Study Week 0 and, change at Study Week 12 from Study Week 8). A mixed model for repeated measures (MMRM) including treatment arm (Lorundrostat and Placebo), sequence (LP and PL) and Treatment Period (Period 1 and Period 2) as fixed effects, subject (sequence), as random (repeated) effect, and baseline (Study Week 0 and Study Week 8) AOBP SBP as a covariate will be used in the analysis. An estimate of the least square means, and the associated standard errors and 90% confidence intervals (CIs) of change from baseline at Study Week 4 will be reported for each arm. The primary analysis will be based on the evaluation of the least square estimate for the treatment arm effect which represents placebo-adjusted effect in lorundrostat treatment periods. Prior to the main estimation, a general linear model with effects of sequence, subject (sequence), period and treatment will be fitted to evaluate the existence of possible carryover/sequence effect.

Statistical approaches for the exploratory endpoints will be described in the statistical analysis plan (SAP).

AEs will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC), preferred term (PT), as well as by severity, causality, and time to occurrence.

Figure 1 Study Flow



* Either study provided commercially available dapagliflozin 10mg QD or continue regularly prescribed SGLT2i
**End of Study: [redacted] OLE will attend a 2week End of Study Safety Followup visit.

Abbreviations: OLE, [redacted]; QD [redacted] LT2 [redacted] 2 [redacted]

Table 1: Schedule of Assessments

Study Period	Screening[1]	Run-in	Randomization[2]	Treatment Period 1 (4 weeks)		Wash Out (4 weeks)	Treatment Period 2 (4 weeks)		EoS[3]	[redacted]
Weeks[5]	-4	-2	0	2	4	8	10	EOT 12	14	[redacted]
Study Visit#	1	2	3	4	5	6	7	8	9	
Informed Consent[6]	X									
Randomization			X							
Demographics	X									
Medical history	X									
Eligibility confirmed	X		X							
Concomitant medications	X	X	X	X	X	X	X	X	X	[redacted]
Physical exam, body weight, height, waist and hip circumference[7]	X		X	X	X	X	X	X	X	[redacted]
Vital signs	X	X	X	X	X	X	X	X	X	[redacted]
AOBP, seated and standing	X		X	X	X	X	X	X	X	[redacted]
12-lead ECG	X		X						X	[redacted]
Serum chemistry (including eGFR, excluding potassium) central lab	X		X	X	X	X	X	X	X	[redacted]
Cystatin-C (central lab)	X		X	X	X	X	X	X	X	[redacted]
Serum potassium (local lab)	X		X[8]	X	X	X	X	X	X	[redacted]
HbA_{1C} (central lab)	X				X			X	X	[redacted]
Hematology (central lab)			X		X			X	X	[redacted]
Urinalysis, spot urine (central lab)	X				X			X	X	[redacted]
Dispense kit for first morning urine void	X	X		X			X			[redacted]
Subject collects first morning urine void, midstream[9]	X		X		X			X		[redacted]
Dispense kit, for 24-hour urine[10]	X	X		X	X		X			[redacted]
Subject collects 24-hour urine[11]		X	X		X	X		X		[redacted]
Pregnancy test[12]	X		X			X		X	X	[redacted]
Adverse events[13]	X	X	X	X	X	X	X	X	X	[redacted]
Study drug dispensed		X[14]	X		X	X				[redacted]
In-clinic dosing			X	X	X	X	X	X		[redacted]
Study drug compliance			X	X	X	X	X	X	X	[redacted]
Biomarkers (central lab)[15]			X		X	X		X	X	[redacted]
Morning serum cortisol[16]	X			X	X		X	X		[redacted]
PK (sampling)[17]				X	X		X	X		
ACTH stimulation test[18]										[redacted]

Abbreviations: ACTH, adrenocorticotropic hormone; AE, adverse event; AESIs, adverse events of special interest; AOBP, automated office blood pressure; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; EoS, End of study; EOT, end of treatment; HbA_{1C}, glycosylated hemoglobin; PK, pharmacokinetics; SAE, serious adverse event; SGLT2i, sodium-glucose cotransporter-2 inhibitor; [redacted].

1 Screening will be 2 weeks. However, if required, the screening window may be extended to 4 weeks without approval from the Medical Monitor.

2 Only subjects who continue to meet all eligibility criteria will be randomized.

3 Visit for subjects not participating in the open label extension study only. Study visit window is ± 5 days.

4 Assessments performed during an unscheduled visit will be done on an as needed basis.

5 Study visit windows (double blind period and run-in) are ± 3 days.

6 Written informed consent must be obtained prior to conducting any study procedures.

7 At the Screening Visit a physical examination will be performed and should include an evaluation of the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems. Height will be measured at Screening only. At other visits, a limited, symptom-directed physical examination should be performed. Any abnormality identified should be recorded either as medical history or AE accordingly.

8 Serum potassium must be collected 3 days prior to Randomization and values must be reviewed by the Investigator for Randomization eligibility.

9 During Screening, one first morning urine void to be brought in, in the first week after Screening to determine eligibility. An unscheduled visit during Screening period for subjects to return first morning void must take place a minimum of 7 days prior to the Run-in visit so that the result is available for eligibility review. The sample needs to be 200-5000 mg/g inclusive to meet eligibility criteria. Samples will be assessed for albumin, protein, and creatinine.

10 Subjects will be given a 24-hour urine collection kit to take home at preceding visits. An aliquot of urine will be retained for future biomarker assessments.

11 Subjects must start urine collection on Day-1 and return the collected 24-hour urine on Week 0 Randomization visit. 24-hour urine samples will be utilized for assessment of albumin, protein, creatinine, sodium, potassium, cortisol, and aldosterone. An aliquot of urine will be retained for future assessments.

12 Women of childbearing potential only. A sample for serum pregnancy test will be collected at Screening. Follicle stimulating hormone must be used to confirm postmenopausal status in all postmenopausal women at Screening. Urine pregnancy tests will be done at other visits. If urine pregnancy test is positive, a serum pregnancy test will be collected to confirm results at the local lab.

13 All AEs and SAEs will be collected from signing of informed consent form until the subject has completed the EoS visit or transitioned to the open label extension study. All AESIs will be collected upon initiation of treatment until the subject has completed the EoS visit or transitioned to the open label extension study.

14 Only for SGLT2i naïve patient or patient switching to sponsor provided SGLT2i.

15 An aliquot of serum will be retained for future biomarker assessments. A sample of whole blood will be collected at Randomization and retained for future proteomic and genomic assessments. A mid-stream urine sample will also be collected for future biomarker analyses. Blood and urine samples will be processed and stored as described in the laboratory manual.

16 Blood draw for cortisol assessment should occur as close to 8 AM as possible on the morning of the study visit.

17 Subjects should have a blood sample drawn just prior to dosing and another blood sample taken 1-2 hrs. post-dose.

18 ACTH (Cosyntropin) stimulation testing to be performed at unscheduled visits if clinically indicated by signs, including serum cortisol below 3 µg/dL, or below 10 µg/dL accompanied by symptoms of hypocortisolism.

2. INTRODUCTION

2.1 Study Rationale

Chronic kidney disease (CKD) is an increasingly prevalent condition globally and is strongly associated with incident cardiovascular disease (CVD, Pugh , 2019). Hypertension is both a cause and effect of CKD and affects many CKD patients (Pugh , 2019). Control of hypertension is important in those with CKD as it leads to slowing of disease progression as well as reduced CVD risk (Fay , 2020). Existing guidelines do not offer a consensus on optimal blood pressure (BP) targets, while the clinical practice guidelines for CKD recommend that for stages 1-4, treatment should focus on comorbid conditions (e.g., hypertension, metabolic acidosis, and hyperkalemia) as opposed to correcting and reversing the damaged kidney function itself (Levin , 2013). As CKD advances, it becomes harder to delay its progression (Pugh , 2019). Therefore, it is vital to develop effective therapeutic treatments aimed at slowing not only the development of CKD, but to target its progression as early as possible. Although patients with hypertension and CKD require a combination of medications to achieve BP and estimated glomerular filtration rate (eGFR) targets, medication is often suboptimal leaving the conditions inadequately treated (Fay , 2020). Together, these issues highlight an unmet need in the treatment of hypertension and CKD.

Mineralys Therapeutics is developing lorundrostat, a selective aldosterone synthase inhibitor (ASI), for the treatment of hypertension in CKD with persistent albuminuria despite treatment by upstream renin-angiotensin-aldosterone system (RAAS) inhibitors including angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB). While the existing class of mineralocorticoid receptor antagonists (MRAs) address the dysregulated biology associated with hypertension, the new ASI class has the potential for a more favorable benefit/risk profile due to the differentiated mechanism of action, which results in a profound decrease in circulating and local aldosterone production, rather than the marked increase seen with the MRA class. In addition, unlike spironolactone, the most commonly prescribed MRA, and other ASIs in development, lorundrostat, because of its short half-life, has the potential to be rapidly reversible should adverse events (AEs), such as hyperkalemia or hypotension, be encountered. In CKD, there is increasing evidence to support the role of sodium-glucose cotransporter 2 inhibitor (SGLT2i) therapy in patients with CKD (Mende , 2022). These therapies do not increase the risks of serious hyperkalemia or severe hypokalemia (Neuen , 2022) suggesting that there may exist a potential synergistic effect of combination therapy with SGLT2i and selective ASIs, such as lorundrostat, to decrease the occurrence of hyperkalemia and slow the progression of kidney disease.

This study will evaluate the efficacy, safety, and tolerability of lorundrostat in addition to a SGLT2i in subjects with hypertension and CKD with albuminuria despite treatment with ACEi or ARB. If successful, lorundrostat will provide the first targeted therapeutic option for patients with hypertension and CKD.

2.2 Background

Hypertension is a leading risk factor for the development of CVD and its prevalence is increasing (Forouzanfar , 2017). Despite increases in awareness and treatment, hypertension continues to be responsible for more years lived with disability and more combined years of life lost than any other cause of morbidity and mortality (Murray , 2013). Reduction in BP reduces the risk for end-organ

damage, and patients who do not reach BP goals, despite multi-drug therapy, are designated as having resistant hypertension (RH, Carey , 2018). Resistant hypertension is common in individuals with CKD and becomes more prevalent with declining kidney function (Tanner , 2013). An analysis of more than 3,300 patients in the Chronic Renal Insufficiency Cohort (CRIC) study, a multicenter prospective observational study of adults with eGFRs of 20 to 70 mL/min/1.73 m^2, found the prevalence of RH among hypertensive patients to be 40.4% (Thomas , 2016).

CKD affects more than 10% of the global population and is one of the leading causes of mortality worldwide (Kovesdy , 2022). According to the United States (US) Center for Disease Control and Prevention (CDC), an estimated 1 in 7 US adults have CKD (CentersDC, 2021). CKD is characterized by the gradual loss of kidney function and can be classified into 5 stages (Levin , 2012). Stage 1 is normal or high functioning (eGFR ≥90 mL/min/1.73 m^2), Stage 2 is mildly decreased (eGFR 60-89 mL/min/1.73 m^2). Stage 3 is divided into 2 additional stages: Stage 3a and 3b. Stage 3a is mildly to moderately decreased (eGFR 45-59 mL/min/1.73 m^2), while Stage 3b is moderately to severely decreased (eGFR 30-44 mL/min/1.73 m^2). Stage 4 is severely decreased (eGFR 15-29 mL/min/1.73 m^2), and the final stage, Stage 5, is kidney failure (eGFR <15 mL/min/1.73 m^2). There is no cure for CKD, and despite multiple treatment options the risk of AEs and disease progression remains high, emphasizing an unmet need in CKD treatment.

Although hypertension is an important cause of CKD (Hanratty , 2011), CKD itself increases BP through several mechanisms, including impaired sodium excretion and premature vascular ageing, which subsequently reduce baroreceptor sensitivity, increase sympathetic nervous tone, and active the RAAS (Pugh , 2019). Aldosterone contributes to the development of kidney disease (Vaidya , 2018), by activating the mineralocorticoid receptor (MR) in kidney cells leading to podocytopathy, tubulointerstitial inflammation, and tubulointerstitial fibrosis (Epstein , 2021). Serum aldosterone concentrations are inversely correlated with the eGFR, positively associated with 24-hour urine protein, and independently associated with progression of CKD and incident end stage renal disease (ESRD) (Verma , 2022). This suggests pathogenic aldosteronism has a role in CKD progression.

A strategy for lowering the aldosterone-related risk for fibrotic kidney disease is the use of ASIs (Weldon and Brown, 2019; Brown, 2020). ASIs could work more effectively than MR blockade as aldosterone not only confers the MR mediated genomic effects but also the non-genomic and MR independent effects leading to kidney fibrosis (Chen , 2013). Clinical development of ASIs has been complicated by difficulties in obtaining sufficient selectivity blocking aldosterone synthase, but not cortisol synthase. The use of ASIs such as lorundrostat to inhibit aldosterone production in the adrenal gland as opposed to blockade of aldosterone activity at the receptor is a promising alternative approach for the treatment of CKD.

A review of trials conducted in patients with CKD showed that there are currently five classes of treatments available to slow CKD progression or reduce eGFR decline (Mende , 2022). These treatments include ACEi, ARBs, SGLT2i, Glucagon-like peptide-1 receptor agonists (GLP1-RAs), and the MRA, finerenone (Mende , 2022). RAAS inhibitors, such as ACEi and ARBs, are commonly used to reduce albuminuria and slow down disease progression in patients with CKD (Mukoyama and Kuwabara, 2022). These therapies have beneficial clinical effects in patients with CKD with and without diabetes (Xie , 2016) and are thought to work in large part by reducing serum and renal aldosterone levels. Although current guidelines recommend the use of RAAS inhibitors (ACEi or ARB) to delay or prevent CKD progression (Mukoyama and Kuwabara, 2022), aldosterone levels often return to pre-treatment levels. This resulting failure of aldosterone suppression is referred to as “aldosterone breakthrough” and can contribute to the development of RH, hyperkalemia, and

progression of cardiovascular and renal diseases (Mogi , 2022; Ando, 2023). Patients are often advised to reduce dosage or even discontinue their treatment (Mukoyama and Kuwabara, 2022). One way to reduce the effect of "aldosterone breakthrough" is by lowering aldosterone production by inhibiting the enzyme aldosterone synthase (Weldon and Brown, 2019; Ando, 2023). Short-term studies in patients with CKD and Type 2 diabetes mellitus (T2DM) have demonstrated promising reductions in albuminuria when MRAs were used as an add-on to an ACEi or ARB. However, these studies also showed an increased incidence of hyperkalemia-related discontinuation in patients treated with MRAs (Bakris, 2020). Finerenone, a selective oral, non-steroidal MRA, has been shown to lower the risk of CKD progression and cardiovascular events in patients with CKD and T2DM (Bakris, 2020).

The standard of care in the treatment of albuminuria has changed recently with many guidelines recommending the addition of an SGLT2i to an ACEi or ARB (Mende , 2022). A review of SGLT2i showed that they can reduce the risk of ESRD in patients with T2DM and CKD (Braunwald, 2022). Data from large, randomized, placebo controlled kidney outcome trials in patients with T2DM (CREDENCE) and in patients with or without T2DM (DAPA-CKD) showed a reduction in the risk of CKD progression with the use of SGLT2i (Perkovic , 2019; Heerspink , 2020). Improvement in the kidney outcomes was also observed in the EMPA-KIDNEY trial in patients with CKD with or without diabetes with the trial being stopped early by the data monitoring committee (DMC) because of positive efficacy (Herrington , 2023). Data from the CREDENCE, DAPA-CKD, and FIDELIO-DKD trials suggest that adding an appropriate SGLT2i or MRA to standard of care RAAS inhibition can improve a range of both kidney and cardiovascular outcomes in patients with or without T2DM (Garcia Sanchez, 2022). SGLT2i do not increase the risk of serious hyperkalemia or severe hypokalemia (Neuen , 2022) suggesting that there may also exist a potential synergistic effect of combination therapy with SGLT2i and selective ASIs such as lorundrostat. Such combination therapy could decrease the occurrence of hyperkaliemia and potentially slow the progression of kidney disease and therefore warrants further investigation.

While the existing class of MRAs address the "aldosterone breakthrough", the new ASI class has the potential for a more favorable benefit/risk profile due to the differentiated mechanism of action, which results in a decrease in circulating and local aldosterone production, rather than the marked increase seen with the MRA class. Lorundrostat, a selective ASI, is an inhibitor of cytochrome P450 11B2 (CYP11B2; aldosterone synthase), which is a rate-limiting enzyme for aldosterone production. The results of a series of pharmacology studies demonstrate that lorundrostat is a selective inhibitor of CYP11B2 and is not associated with adverse effects upon the central nervous, respiratory, or cardiovascular systems. Unlike spironolactone, the most commonly prescribed MRA, and other ASIs in development, lorundrostat, because of its short half-life, has the potential to be rapidly reversible should AEs such as hyperkalemia or hypotension be encountered. Data from both a Phase 1 study in healthy subjects (NCT02953132) and a Phase 2 study in patients with uncontrolled hypertension, Target-HTN (NCT05001945), have shown lorundrostat to have acceptable safety profile and be well tolerated.

2.3 Benefit/Risk Assessment

2.3.1. Benefit and Risk Assessment for Lorundrostat

Clinical data obtained from healthy volunteers as well as patients with uncontrolled hypertension and RH have shown that lorundrostat has been well tolerated and has an acceptable safety profile.

2.3.1.1. Risk of Hyperkalemia

Increased potassium levels have been observed in non-clinical studies of lorundrostat and are a known risk of MRAs, in general. Early healthy volunteer studies with lorundrostat revealed a trend of mild increase in serum potassium, although none of these increases were assessed as clinically significant. In a Phase 2 study in [redacted] subjects with uncontrolled hypertension (MLS-101-201), hyperkalemic events were the most frequently reported AEs. Adjusting the event rate to censor values that failed quality control criteria designed to rule out non-reproducible and factitious hyperkalemia (e.g., elevated lactate dehydrogenase (LDH), with the failure to reproduce in a second blood sample drawn as soon as possible while the subject was on the same dose of lorundrostat), the number of events and subjects, presented as n events (N individuals) deemed as mild, moderate and severe laboratory abnormalities were: [redacted] respectively. In all cases, an electrocardiogram (ECG) was obtained and in no case were clinically significant abnormalities identified.

In this study, to mitigate potential risks associated with hyperkalemia, subjects will be required to have a serum potassium of [redacted] prior to starting investigational drug and return to the clinic regularly to assess potassium levels locally at each in-clinic visit following initiation of treatment with lorundrostat. Clinical monitoring will allow early detection of potential AEs or trends that may be concerning, particularly those associated with increasing potassium levels.

2.3.1.2. Risk of Hyponatremia

A clinically insignificant decrease in serum sodium was observed in early healthy volunteer studies with lorundrostat. In the completed Phase 2 study of lorundrostat (MLS-101-201), there were 2 episodes of hyponatremia reported. One episode of severe hyponatremia occurred in a subject randomized to the lorundrostat 100 mg QD dose cohort. The subject had a past history of chronic mild hyponatremia, with serum sodium values of [redacted] in the two weeks prior to Randomization. One week after Randomization, serum sodium was [redacted] and after two weeks it was [redacted] There were no symptoms or abnormal physical findings. After discontinuation of study medication, serum sodium levels returned to a maximum value of [redacted]/L and remained between [redacted] mmol/L over the subsequent five weeks of observation with no active treatment measures or hospitalization required. The other event was an episode of moderate hyponatremia in a subject dosed with 100 mg QD and a baseline sodium level of [redacted] which declined to a value of [redacted] at week 4 of treatment and increased to [redacted] over the following four weeks after dose reduction to lorundrostat 50 mg QD. Muscle cramps were the only symptom reported, responding to brief treatment with ropinirole.

To mitigate potential risks associated with hyponatremia, subjects with a history of clinically significant hyponatremia within 1 year prior to Screening will be excluded. Frequent monitoring of serum electrolytes, including serum sodium with Medical Monitor oversight will occur throughout the study.

2.3.1.3. Risk of Hypotension and Dizziness

In healthy subjects, the incidence of dizziness/postural dizziness was slightly higher among lorundrostat treated subjects compared to placebo subjects.

Furthermore, hypotension with symptoms was seen in [redacted] who received lorundrostat in the Phase 2 study of subjects with uncontrolled hypertension (MLS-101-201). These events were

reversible with treatment cessation as expected based on the mechanism of action of lorundrostat. In addition, 3 subjects developed orthostatic hypotension in the absence of seated hypotension, defined as a fall of 20 mmHg in systolic BP (SBP) or 10 mmHg in diastolic BP (DBP) when going from sitting to standing position. In each case, the hypotensive episode resolved spontaneously and did not recur for the remainder of the treatment period. Two of these events were assessed by the Investigator as unlikely to be related to study medication; one event was assessed as possibly related.

Subject BP, in both seated and standing positions, will be regularly assessed throughout the course of this study. Investigators will be instructed to treat hypotensive episodes in accordance with the standard of care at the site/institution and medical guidelines.

2.3.1.4. Risk of Cortisol Suppression or Overproduction

No events of clinically significant serum cortisol reduction or impaired adrenocorticotropic hormone (ACTH) stimulated cortisol production have been observed in completed clinical trials to date.

In the Phase 2 trial in subjects with uncontrolled hypertension, a small increase in morning serum cortisol following 8 weeks of treatment was observed in most active drug cohorts, as well as in placebo treated subjects. Three subjects in the 100 mg once daily (QD) cohorts had a morning serum cortisol value above the normal range. These increases were modest and not associated with symptoms or signs of clinical hypercortisolism.

In this present trial, all subjects will be monitored for signs and symptoms of hypercortisolism. In addition, subjects will have their serum cortisol measured regularly, with the blood draw performed as close to 8 AM as possible. If necessary, a 24-hour urinary free cortisol assessment and unscheduled ACTH stimulation test will be performed.

Specific entry and dose modification criteria have been added to the protocol to minimize potential risk for subjects.

Benefit and Risk Assessment for Dapagliflozin

For full benefits and risks associated with dapagliflozin please refer to the most recent package inserts for the product.

2.3.1.5. Risk of Hypotension

Symptomatic hypotension may occur after initiating dapagliflozin particularly in subjects with impaired renal function [redacted] elderly subjects [redacted]5 [redacted] in subjects with low SBP, and in subjects on diuretics. Before initiating dapagliflozin, volume status will be assessed and corrected if indicated. Subjects will be educated on the symptoms of hypotension and volume depletion and will be monitored at least every 3 weeks (and more frequently if indicated) for signs and symptoms of hypotension after initiating therapy, as indicated above for lorundrostat.

2.3.1.6. Risk of Ketoacidosis

Ketoacidosis has been reported infrequently (estimated to be no greater than [redacted] in diabetic subjects taking SGLT2i, including rare fatal cases. Subjects with a history of at least 1 severe hypoglycemic event or severe diabetic ketoacidosis event in the 12 months prior to Screening will be excluded from

the trial. Subjects will be monitored for signs and symptoms of ketoacidosis, as well as predisposing conditions such as volume depletion.

2.3.1.7. Risk of Acute Kidney Injury and Impairment in Renal Function

There have been post marketing reports of acute kidney injury, some requiring hospitalization and dialysis in patients receiving SGLT2i. Otherwise, small clinically insignificant and reversible decreases in eGFR are commonly observed following the initiation of SGLT2i and are likely related to mild volume depletion. Many of these episodes may have been related to volume depletion, congestive heart failure (CHF) and ketoacidosis. Subjects with severe CHF, ketoacidosis and need for renal replacement therapy will be excluded. Subjects will be monitored for signs and symptoms of acute kidney injury.

2.3.1.8. Risk of Hypoglycemia

Hypoglycemia is a rare finding in non-diabetic subjects. A recent systematic review of SGLT2i (Teo 2021) found the incidence of hypoglycemia in non-diabetics was [redacted]. Adding SGLT2i to the T2DM treatment regimen is expected to lower blood glucose level and may cause hypoglycemia. All subjects will be monitored for signs and symptoms of hypoglycemia. Subjects with T2DM may be instructed to monitor their blood glucose level more closely upon initiation of study drug. Baseline treatment for T2DM will be adjusted, as needed, to avoid hypoglycemia.

2.3.1.9. Risk of Urosepsis and Pyelonephritis, Lower Limb Amputation, Genital Mycotic Infections, Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)

All these conditions were observed rarely in clinical trials of SGLT2i. Subjects with a history of these conditions will be excluded from this study. All subjects will be monitored for the signs and symptoms of these conditions.

2.3.1.10. Other Risks

Additional risks for study subjects may include but are not limited to:

- Complications arising from study assessments (e.g., drawing blood may cause temporary discomfort from the needle stick, bruising, bleeding, and, rarely, infection),
- Increased risk of exposure to pathogens causing infectious diseases from regular clinic visits, including coronavirus disease 2019 (COVID-19),
- A risk of loss of confidentiality.

2.3.1.11. Potential Benefits

Benefits for study subjects may include but are not limited to:

- Potential benefit of receiving study treatment,
- Contribution to the process of developing/improving the therapies for an unmet medical need,
- Medical evaluations/assessments (e.g., physical exam, ECG, laboratory assessments).

2.3.1.12. Overall Benefit-Risk Conclusion

Considering the measures taken to minimize risk to subjects participating in this study, the potential risks are justified by the anticipated benefits that may be afforded to subjects with hypertension and CKD.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

3.1.1. Primary Objective

- To assess the effect of lorundrostat 25 mg QD, in addition to a SGLT2i, on systolic blood pressure (SBP) in subjects with hypertension and CKD with albuminuria on stable treatment with an ACEi or an ARB

[redacted]

- [redacted]
- [redacted]
- [redacted]
- T[redacted] k[redacted] D[redacted] LT2[redacted]

3.1.3. Safety Objective

- To investigate the safety and tolerability of lorundrostat, in addition to a SGLT2i, in subjects with hypertension and CKD with albuminuria on stable treatment with an ACEi/ARB

[redacted]

[redacted]

3.2 Study Endpoints

3.2.1. Primary Endpoint

- Placebo-adjusted change from baseline in automated office blood pressure (AOBP) SBP at Study Week 4

[redacted]

3.2.3. Safety Endpoints

- Incidence and severity of AEs
- Clinically significant changes in vital signs (body temperature, heart rate, and respiratory rate), physical examination and ECG parameters
- Clinically significant changes in clinical laboratory assessments (hematology, chemistry, and urinalysis)
- Incidence of AEs of Special Interest (AESI)
    - Modification of study drug dose due to hyperkalemia (e.g., dose reduction, dose hold, or permanent dose discontinuation)
    - Modification of study drug dose due to hyponatremia (e.g., dose reduction, dose hold, or permanent dose discontinuation)
    - Hypotension with symptoms (e.g., light-headedness, dizziness, presyncope, or syncope)
    - Severely elevated BP (AOBP SBP >180 mmHg or AOBP DBP >110 mmHg)
    - Modification of study drug dose due to hypercortisolism (morning serum cortisol >35 µg/dL, confirmed by 24-hour urinary free cortisol)
    - Discontinuation of study drug due to hypocortisolism confirmed by ACTH stimulation test
    - Overdose of study drug

- Modification of study drug dose due to reduction in kidney function (e.g., dose reduction, dose hold, or permanent dose discontinuation)

[redacted]

4. STUDY DESIGN

4.1 Overall Study Design

This is a randomized, double-blind (DB), placebo controlled, crossover study with a two-period, two-sequence (2x2) design evaluating the efficacy and safety of 25 mg QD lorundrostat (an ASI) in addition to a SGLT2i for the treatment of hypertension in subjects with CKD and albuminuria despite receiving stable treatment with an ACEi or an ARB. Subjects will be at least 18 years old with hypertension (AOBP SBP 135-180 mmHg inclusive at Randomization), and mild to severe CKD (eGFR ≥30 mL/min/1.73 m^2) with albuminuria (UACR 200-5000 mg/g, inclusive) at the Screening Visit. The study consists of a 2-week screening period, a 2-week run-in period where subjects will either begin study provided dapagliflozin 10 mg or continue on their regularly prescribed SGLT2i, and two DB 4-week treatment periods separated by a 4-week washout period (Figure 1). Subjects will be randomized (1:1) to two treatment sequences: lorundrostat-placebo (LP) and placebo-lorundrostat (PL).

Treatment allocation will be organized as follows:

- Treatment Period 1 (DB Study Week 0 to Study Week 4): Subjects will receive a lorundrostat 25 mg (sequence LP) or one matching lorundrostat-placebo tablet (sequence PL) dosed orally QD.
- Washout (Study Week 4 to Study Week 8): All subjects will receive matching placebo dosed orally QD.
- Treatment Period 2 (DB Study Week 0 to Study Week 4): Subjects will receive one matching lorundrostat-placebo tablet (sequence LP) or a lorundrostat 25 mg (sequence PL) dosed orally QD.

During the DB and Washout periods, subjects will continue their background therapy including ACEi/ARB and SGLT2i.

If at any time during DB eGFR drops by ≥30% from Randomization, a decision on dose reduction, dose hold or dose discontinuation will be made in consultation between the Investigator and the Medical Monitor.

Following the completion of the study, subjects will be offered the opportunity to participate in a separate open label extension (OLE) study. If subjects do not enter the OLE, a final End-of-Study (EoS) safety visit will take place 2 weeks after the last dose of study drug.

4.2 Scientific Rationale for Study Design

Although there is widespread availability of inexpensive and effective oral BP-lowering medications, rates of hypertension control are poor irrespective of age, race, or sex (Virani, 2021). There is currently no cure for CKD and despite multiple treatment options, the risk of AEs and CKD progression remains high (Bakris, 2020). Together, these issues highlight an unmet need in the treatment of hypertension and CKD.

Lorundrostat is an inhibitor of CYP11B2 (aldosterone synthase), which is a rate-limiting enzyme for aldosterone production. In the Phase 2 Target-HTN (MLS-101-201) study, patients with uncontrolled hypertension demonstrated clinically relevant reductions in SBP following 8 weeks of treatment with lorundrostat when compared to placebo leading to a beneficial, reversible, dose-dependent reduction in

eGFR (Mineralys Therapeutics, NCT05001945). The selectivity of lorundrostat for aldosterone inhibition was confirmed as cortisol levels were not inhibited across the range of doses. This Phase 2 study will evaluate the efficacy, safety, and tolerability of lorundrostat in addition to SGLT2i in subjects with hypertension and CKD with persistent albuminuria despite treatment with an ACEi or ARB.

The study is designed as a DB randomized crossover study. A crossover design is selected as more efficient due to avoidance of between-subject variation and consequent lower total sample size requirement. Available data suggest reversibility of BP after short-term treatment with lorundrostat. Reversibility, combined with a 4-week single-blind placebo washout period minimize possibility of carryover effect to treatment Period 2. Use of placebo control period is justified with short duration of the trial and clinical equipoise. Placebo control allows for an unbiased assessment of treatment efficacy.

4.3 Number of Subjects / Number of Centers

Approximately 60 subjects will be enrolled in approximately 30-40 investigational centers in the US.

4.4 Study Duration

The expected duration of the study for each subject from Screening to the End of Study visit is expected to be approximately 18 weeks.

4.5 Justification for Dose

This study will evaluate the safety, hypertension, and albuminuria-lowering effect of lorundrostat dosed orally to a maximum of 25 mg QD.

The dose is based on the results of a Phase 1 first-in-human study (MT-4129-E01) and a Phase 1 study in subjects with normal renal function and subjects with severe renal impairment (MLS-101-005), and a Phase 2 dose ranging trial in subjects with uncontrolled hypertension (MLS-101-201).

In MT-4129-E01 single doses of lorundrostat up to 800 mg, and multiple doses of lorundrostat up to 360 mg/day, taken orally QD for 7 days, were evaluated in healthy subjects. No dose-limiting toxicities were observed. Dizziness/dizziness postural was reported by 9 out of 87 (10.3%) of lorundrostat-treated subjects compared to 1 out of 29 (3.4%) placebo subjects across all cohorts with no apparent dose relationship.

Post-dose serum potassium concentrations >5.0 mmol/L were observed in 13 subjects (14.9%) who received lorundrostat (6 subjects in the single ascending dose [SAD] cohort and 7 subjects in the multiple ascending dose [MAD] cohort) across all cohorts. Only 2 of these 13 subjects had post-dose serum potassium concentration >5.5 mmol/L (one subject with a post-dose serum potassium concentration >6.0 mmol/L). None of the serum potassium elevations were considered clinically significant, and there was no dose-dependent trend. There were no clinically significant findings with respect to vital signs, ECGs, or physical examinations.

In MLS-101-005, single oral doses of 100 mg lorundrostat were safe and well tolerated by subjects with severe renal impairment (n = 8, eGFR <30 mL/min) and subjects with normal renal function (n = 9, eGFR ≥90 mL/min). There was no statistically significant effect of renal impairment on the pharmacokinetics (PK) of lorundrostat or the metabolite MLS-102, based on area under the curves

(AUCs) and maximum observed plasma concentration (C_{max}). There were no deaths, serious adverse events (SAEs) or significant treatment-emergent adverse events (TEAEs) reported in the MLS-101-005 study.

In the MLS-101-201 Phase 2 study, a statistically significant placebo-adjusted reduction in SBP at Week 8, as measured by AOBP, of 9.6 mmHg (p = 0.0114) and 7.8 mmHg (p = 0.042) was observed in the 50 mg QD and 100 mg QD cohorts, respectively.

Treatment-emergent SAEs were reported in three subjects, one of which was deemed to be possibly related to lorundrostat in a subject with worsening of pre-existing hyponatremia, which reversed after treatment discontinuation. The two active QD doses saw modest increases in potassium levels across the cohorts of 0.25 mmol/L with the 50 mg QD and 0.29 mmol/L with the 100 mg QD dose. Six subjects experienced transient elevated serum potassium greater than 6.0 mmol/L, none of which were considered an SAE, and all rapidly resolved after discontinuation or dose adjustment, which is consistent with the short half-life of lorundrostat. One of the events was assessed as erroneous due to sample misprocessing. As anticipated, and in a manner similar to ACEi and ARB, the BP lowering effect of lorundrostat led to a beneficial, reversible dose-dependent reduction in eGFR, Finally, the selectivity of lorundrostat for aldosterone inhibition was confirmed as cortisol levels were not observed to be inhibited across the range of doses. There were no notable findings in terms of vital signs, physical examination, or ECG parameters.

This study may also provide commercially available dapagliflozin 10mg QD for subjects naïve to SGLT2i or who elect to take study provided dapagliflozin in lieu of their regularly prescribed SGLT2i. Dapagliflozin 10 mg has been chosen because it is the dose that is Food and Drug Administration (FDA)-approved to reduce the risk of sustained eGFR decline, end stage kidney disease, cardiovascular death, and hospitalization for heart failure in adults with CKD at risk of progression in patients with eGFR ≥25 mL/min/1.73 m^2. This dose has also been demonstrated to reduce albuminuria in diabetic and non-diabetic patients with CKD in the DAPA-CKD trial (Jongs 2021).

4.6 End of Study Definition

The end of study is defined as the date of the last visit of the last subject in the study. A subject is considered to have completed the study if they have completed all periods of the study from Screening up to and including the EoS visit for those subjects not who will not participate in the OLE. Subjects who withdraw prematurely from the study will attend an EoS visit and will not be eligible to progress to the OLE study.

At the time of study completion or EoS visit, subjects will be queried regarding any AEs, concomitant medications, and concurrent procedures, which will be recorded on the appropriate page(s) of the source documents and electronic case report form (eCRF). At the final study visit, subjects with ongoing AEs that are considered by the Investigator to be serious, study drug-related, or associated with the target condition will be requested to continue to follow up with the Investigator until the AE resolves, is stable, or follow-up is no longer possible/necessary. Any death or pregnancy that occurs while on study (or, for subjects not participating in the OLE study, within 28 days after the subject's last dose of study drug) must be reported to the Sponsor/designee for the study within 24 hours after the center becomes aware of the event.

4.7 Criteria for Study/Site Termination

Both the Sponsor and the Investigator reserve the right to terminate the study according to the study contract. The Sponsor may issue a protocol amendment or discontinue the study entirely, based on regulatory authority or Institutional Review Board/Independent Ethics Committee (IRB/IEC) recommendations, drug safety or availability concerns, discontinuation of the development program for lorundrostat, or at the Sponsor's discretion, with at least 30 days' notice. The DMC may also recommend study termination based on a review of the safety data.

4.8 Study Conduct

A schedule of study assessments is presented in the Schedule of Assessments (**Table 1**). Details of study assessments are provided in the Study Reference Manual (SRM) and Section 8 of this protocol.

4.9 Modifications to Study Conduct Due to Global Pandemics

In an aftermath of the COVID-19 pandemic that has had a worldwide impact, some modifications to study conduct during a global epidemic/pandemic including, but not limited to, COVID-19 may be necessary to ensure study continuity, including conducting virtual visits when on-site study visits are considered not feasible. Such modifications in study conduct must always be in accordance with local regulations/mandates.

The following are allowable, as necessary, modifications to study conduct during a global epidemic/pandemic:

- Prior to a study visit at the site, the subject may be contacted and screened for potential exposure or infection to any pathogen associated with a global epidemic/pandemic, including but not limited to COVID-19, per site, local, or federal requirements. If the subject is suspected to be exposed to or infected with such a pathogen, the on-site visit should either be rescheduled or a virtual visit may be performed instead, if feasible.
- If a subject cannot attend their regularly scheduled study visits in person due to an exposure to or an infection with any pathogen associated with a global epidemic/pandemic, the Investigator may consider performing safety and efficacy assessments by phone or video, if feasible. Virtual assessments may include home BP evaluation, AEs, and concomitant medication review. Virtual assessments should be recorded by site staff in the source documents.
- Clinical laboratory and pregnancy tests may be performed by local laboratory, if sample collection cannot be performed at the study site due to limitations associated with a global epidemic/pandemic (e.g., site closure). Abnormal laboratory results should be promptly communicated to the Medical Monitor. Subjects' confidentiality must be maintained when communicating results to the Medical Monitor.
- At home study drug administration may continue for up to 2 weeks (at multiple times during the study if required due to a global epidemic/pandemic, although not consecutively) if the subject has no relevant clinically significant out of range values per previous laboratory reports.
- Source documentation should note that the visit was performed virtually and note the name of the local laboratory where laboratory tests were done, if applicable.
- If certain study procedures or assessments (e.g., laboratory tests, vital signs, physical examinations) cannot be completed per the Schedule of Assessments due to a global

epidemic/pandemic, the reason for the missed assessment must be noted in the source documentation, captured in the protocol deviations documentation, and reported to the IRB/IEC if applicable.

A detailed assessment of risks and risk mitigation measures related to any pathogen associated with a global epidemic/pandemic including, but not limited to, COVID-19, should be documented in the appropriate study documents, as applicable.

5. STUDY POPULATION

Subjects not meeting all inclusion criteria, or meeting at least one exclusion criterion, may be re-screened if there is a reasonable probability of reversal. Retesting of laboratory samples, and a repeat AOBP assessment is allowed in the event of technical failure. Inclusion in the study of any subject who meets all eligibility criteria on rescreening will be at the discretion of the Investigator.

5.1 Inclusion Criteria

Subjects eligible for inclusion in this study must meet **all** the following criteria:

1. Written informed consent, obtained before any study-related assessment is performed
2. At least 18 years of age at the time of signing the informed consent form (ICF)
3. At Screening, UACR of 200-5000 mg/g, inclusive, in first morning urine void
4. At Screening, eGFR of ≥30 mL/min/1.73 m^2
5. At Screening, AOBP SBP of 135-180 mmHg, inclusive
6. At Randomization, AOBP SBP of 135-180 mmHg, inclusive
7. On a stable treatment with an ACEi or ARB for at least 4 weeks prior to Screening
8. At Screening, serum cortisol (morning measurement, blood draw as close to 8 AM as possible between 3 and 22 µg/dL, inclusive)
9. At Screening, body mass index (BMI) of ≥18 kg/m^2
10. Fertile male subjects and female subjects of childbearing potential must agree to use an acceptable method of contraception (Appendix 12.4) from the Screening Visit to 28 days after the last dose of study drug in each study part
11. Willing and able to comply with the study instructions and attend all scheduled study visits, and are capable of providing informed consent

5.2 Exclusion Criteria

Subjects meeting any of the following criteria are **not** eligible for inclusion in this study:

1. Women who are pregnant, plan to become pregnant, or are breast-feeding
2. Subjects with known hypersensitivity to lorundrostat or any of its respective excipients
3. Subjects with known hypersensitivity to dapagliflozin or any of its respective excipients (subjects beginning dapagliflozin only)
4. Treatment, or anticipated treatment, with any prohibited medication within the timeframes described in Section 6.9 of this protocol.
5. Treatment, or anticipated treatment, with triamterene and amiloride
6. Participation in a trial involving an investigational device or drug within 4 weeks or 5 half-lives (whichever is longer) prior to the Screening Visit
7. Previous treatment with lorundrostat or other ASI within 4 weeks or 5 half-lives (whichever is longer) prior to the Screening Visit

8. At Screening, serum potassium >5.0 mmol/L
9. At Randomization, serum potassium >5.0 mmol/L (prior to first dosing of study drug)
10. At Screening, serum sodium <135 mmol/L (corrected for hyperglycemia using the Katz formula). Rescreening of subjects with an exclusionary serum sodium is only allowed if two consecutive measurements at least one week apart are ≥135 mmol/L
11. Total bilirubin >2x upper limit of normal (ULN) except for those with a diagnosis of Gilbert's syndrome, unless approved by Medical Monitor
12. History of clinically significant hyponatremia within 1 year prior to Screening
13. History of adrenal insufficiency or an abnormal ACTH stimulation test within 1 year prior to Screening
14. Hospitalization for the treatment of urgent or emergent hypertension within 1 year prior to Screening
15. Current, known or presumed white coat hypertension/significant white coat effect (as defined in the SRM)
16. Current, known or presumed orthostatic hypotension
17. Current, known or presumed autonomic dysfunction
18. Arm circumference >55 centimeters at Screening
19. Subjects with a previously proven secondary cause of hypertension are excluded with the following exceptions:
    a. Subjects with documented sleep apnea are eligible to participate
    b. Subjects with documented primary hyperaldosteronism are eligible to participate if they discontinue use of a MRA. They should have <20 mmHg increase in AOBP SBP, and AOBP SBP <150 mmHg at Randomization. MRA treatment may be tapered over a one-week period.
20. Use of epithelial sodium channel (ENaC) inhibitors or MRAs, including, but not limited to amiloride, triamterene, spironolactone, eplerenone, finerenone, from 4 weeks prior to the Screening Visit and during study participation. With the exception of MRAs in primary aldosteronism.
21. Medical history of kidney disease related to autoimmune diseases (lupus, anti-neutrophil cytoplasmic antibody [ANCA] vasculitis), multiple myeloma or other known paraproteins, infiltrative diseases of the kidney, obstructive nephropathy, cystic kidney diseases, and renal transplantation
22. Medical history of advanced liver disease, including cirrhosis
23. Medical history of active autoimmune disease or recent (within 30 days) or anticipated need for immunosuppressive therapy
24. Subjects with a medical history of urosepsis and pyelonephritis, lower limb amputation, genital mycotic infections, necrotizing fasciitis of the perineum (Fournier's Gangrene)
25. History of heart failure, myocardial infarction, stroke, or transient ischemic attack within 6 months prior to Screening. Heart failure of New York Heart Association (NYHA) Class II or more requires approval by the Medical Monitor

26. Diabetes mellitus with a glycosylated hemoglobin (HbA_{1c}) >10% (>86 mmol/mol) at Screening
27. Planned major surgery requiring hospitalization during the study period or performed within 4 weeks prior to the Screening Visit
28. History of malignant neoplasms within the 5 years prior to Screening except for known history of basal and squamous cell skin cancer and any carcinoma *in-situ*
29. Known or suspected abuse of illicit drugs or alcohol within 1 year prior to the Screening Visit
30. In the opinion of the PI, any other condition that will preclude participation in the study

5.3 Modification of Diet and Glucose Control

Brief dietary counseling reflecting the current standard of care will be provided to all subjects including low potassium diet in subjects with CKD.

For subjects with T2DM entering the study, the PI will evaluate the subject's current diet, diabetes treatment regimen and glucose monitoring regimen with the subject prior to Randomization to determine whether modification of any of these are required in view of the potential initiation of dapagliflozin.

For subjects who are on insulin treatment and/or metformin and are prone to hypoglycemic events based on the subject's medical history, additional glucose monitoring should be incorporated into their standard of care as determined by the PI and if clinically indicated.

5.4 Lifestyle Considerations

5.4.1. Caffeine, Alcohol, and Tobacco

Subjects will abstain from ingesting caffeine or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for at least 30 minutes before the start of any study-related BP measurement.

Subjects will abstain from alcohol for at least 30 minutes before the start of any study-related BP measurement.

Subjects will abstain from smoking and the use of cannabis-derived or nicotine-containing products (including nicotine patches, gums, and e-cigarettes) for at least 30 minutes before the start of any study-related BP measurement.

5.4.2. Activity/Exercise

Subjects will abstain from strenuous exercise for at least 30 minutes before the start of any study-related BP measurement and for 24 hours before each blood collection for clinical laboratory tests. Subjects may participate in light recreational activities (e.g., watching television, reading).

6. STUDY DRUG ADMINISTRATION AND MANAGEMENT

The study drug products for this study are lorundrostat as well as the matching placebo. Additionally, commercially available dapagliflozin will be provided to SGLT2i naïve subjects or those that wish to switch to study provided SGLT2i. Subjects may also choose to stay on their currently prescribed SGLT2i.

The formulation and the manufacturing of study drug follows generally accepted standard procedures. The description, covering in detail all aspects regarding quality and safety of study drug product is part of the Investigator's Brochure (IB) for lorundrostat and product prescribing information for dapagliflozin (FARXIGA®) (FDA Reference ID: 4788803).

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Abbreviations: HBr, monohydrobormide; IMP, investigational medicinal product; QD, once daily.

All packaged tablets will be assigned a unique identifying number, used by the Randomization and trial supply management (RTSM) system to identify the content but maintaining the blind. The test materials will be identified by the lot, batch numbers, retest date, and certificate of analysis.

6.2 Dosing and Administration

During the study all subjects will take the same number of tablets, regardless of treatment allocation, to maintain the blind. Subjects will be instructed to take the tablets orally QD at approximately the same time each morning.

6.3 Preparation, Handling, Storage, Accountability

6.3.1. Study Drug Preparation

Not applicable.

6.3.2. Study Drug Packaging and Labeling

Study drug will be labelled, packed, and released in accordance with all applicable laws, regulations, and administrative provisions relating to the implementation of good manufacturing practice and good clinical practice in the conduct of clinical trials on medicinal products for human use.

Lorundrostat and matching placebo tablets are packaged in 30 count 60 cc white round high density polyethylene bottles with a child-resistant cap. As the study is a DB study, labeling of the lorundrostat and matching placebo tablets/capsules packaging will not show the treatment allocation. All other information required by regulation will appear on the label.

6.3.3. Study Drug Handling and Disposal

All study drug supplies are to be used only for this clinical study and not for any other purpose. Authorized study personnel must maintain a full record of study drug disposition (i.e., a log by date received, dispensation date and subject, date of return from the subject, and detailed study drug usage by each study subject).

After reconciliation, used study drug will be handled according to instructions provided by the Sponsor. At study conclusion, all remaining unused supplies will be similarly handled. Authorized study personnel will record any unaccounted supplies in the final accountability records.

6.3.4. Study Drug Storage

The study drugs should be stored at room temperature (59°F to 77°F [15°C to 25°C]) in an approved storage area with access limited to authorized study personnel.

6.3.5. Study Drug Accountability

Study drugs (including placebo) will be maintained under adequate security by appropriate site personnel (e.g., pharmacist) and in accordance with applicable regulatory requirements. Study drugs remaining at the end of the study will be returned to the Sponsor or their representative or destroyed on behalf of the Sponsor.

The Investigator or designee must maintain adequate records of receipt and distribution of all study drug, using appropriate accountability records.

6.4 Randomization and Blinding

Subjects will be randomized (1:1) to two treatment sequences: LP and PL. Randomization sequence numbers and study drug supplies will be assigned using RTSM. Access to the Randomization sequence codes will be controlled and documented.

The identity of study drug assignments (lorundrostat or placebo) during the DB treatment periods will be concealed from the Investigator, the subject, research center staff, and all personnel involved in the conduct of the study, with the exception of the unblinded Sponsor drug management staff who will oversee the study drug allocations and RTSM/dispensing compliance at the study centers.

Except when it is essential for the medical management of the subject, unblinding the treatment assignment will be considered a protocol deviation. Emergency treatment allocation information will be available by secured access to the RTSM system. If possible, the Investigator should contact the Sponsor before unblinding any subject's treatment assignment. If this is not possible, the Sponsor should be notified within 24 hours after the unblinding event. After unblinding, the subject will be discontinued from study drug treatment, but will continue participation in the study, including participation in all remaining visits and assessments, until the EoS visit. The reason for unblinding must be documented in the eCRF.

6.5 Study Drug Compliance

Compliance with study drug dosing will be assessed at each visit. Compliance will be assessed by direct questioning and counting returned tablets during the site visits and will be documented in the source documents and relevant case report form. Deviation(s) from the dosage regimen should be recorded.

A record of the quantity of study drug dispensed to and administered by each subject must be maintained and reconciled with study intervention and compliance records. Study drug start and stop dates, including dates for study drug holds and/or dose reductions will also be recorded.

Study drug compliance will be defined by the treatment compliance ratio: The number of doses taken by the subject divided by the number of doses dispensed. Compliance is defined as taking between 75% and 125% of the study drug provided.

This study may use a medication adherence monitoring platform. The platform will be provided on a smartphone application. Built-in reminders and a communication system allow real-time intervention in case of missed doses, reinforce the proper dosing schedule, and improve data integrity.

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6.7 Safety Criteria for Dose Adjustment or Discontinuation of Study Drug

If, at any time during the study, a subject experiences a clinically significant laboratory or medical assessment (e.g., hyperkalemia, hyponatremia, symptomatic hypotension, severely elevated BP,

hypercortisolemia, hypocortisolemia, reduction in kidney function), laboratory test results will be confirmed using a local laboratory and AOBP measurements will be repeated. At the discretion of the Investigator, in consultation with the Medical Monitor, the dose of the study drug may be modified, or temporarily or permanently discontinued. The Investigator may temporarily interrupt study drug without prior consultation with the Medical Monitor at their discretion and discuss their decision and whether the interruption should be converted to a discontinuation with the Medical Monitor within 24 hours. A subject with modification of their study drug will not be withdrawn from the study.

6.8 Concomitant Therapy

Any medication or vaccine (including over the counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the subject is taking at Screening or takes during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

6.9 Prohibited Treatments

The following medications are prohibited from the Screening Visits until the End of Treatment (EOT), unless otherwise stated:

- Previous treatment with lorundrostat or other ASI within 4 weeks or 5 half-lives (whichever is longer) prior to the Screening Visit.
- Use of ENaC inhibitors or MRAs, including, but not limited to amiloride, triamterene, spironolactone, eplerenone, finerenone, from 4 weeks prior to the Screening Visit and during study participation. With the exception of MRAs in primary aldosteronism.
- Use of anti-hypertensive medications (AHT) medications other than lorundrostat and those already prescribed at the Screening Visit, for the duration of study participation, require approval of the Investigator, followed by reporting to the Medical Monitor. Consultation with the Medical Monitor is recommended.
- Sympathomimetic decongestants on the morning of any study-related BP assessment.
- Chronically administered oral corticosteroids from 3 months prior to the Screening Visit and during study participation. Short-term (i.e., ≤2 weeks) use of topical corticosteroids is allowed if taken for ≥1 month prior to Randomization. Intramuscular steroids from 3 months prior to the Screening visit until completion of study participation. Inhaled and intra-ocular corticosteroids are allowed.
- Short-acting nitrates taken for angina or for underlying cardiac disease during study participation are allowed but should be monitored and study drug discontinued if symptoms of hypotension or orthostatic hypertension occur or SBP <110 mmHg is documented. Chronic, long-acting doses of nitrates are acceptable.
- Enrollment of subjects requiring treatment with strong CYP3A and CYP3A4 inducers (e.g., apalutamide, carbamazepine, enzalutamide, fosphenytoin, lumacaftor, mitotane, phenobarbital,

phenytoin, primidone, rifampin, St. John's Wort) must be approved by the Medical Monitor. Moderate inducers of CYP3A and CYP3A4 are acceptable.

- Use of Proton Pump Inhibitors (PPIs) for more than 3 days per week. These must be abstained for at least 5 days prior to a scheduled visit.
- Use of digoxin is allowed, but levels should be monitored.

The decision to administer a prohibited medication/treatment during the study period is done with the safety of the subject as the primary consideration. Consult with the Medical Monitor for continued evaluation of study eligibility.

7. DISCONTINUATION / WITHDRAWAL CRITERIA

7.1 Discontinuation of Study Drug

Subjects who wish to stop treatment for any reason may stop at any time during the study.

Reasons for discontinuing study drug may include:

- Unavoidable use of prohibited/excluded medications (see Section 6.9)
- Administrative decision by the Investigator or the Sponsor
- Chronic or repeated subject noncompliance with the study drug dosing schedule (see Section 6.5)
- Development of an AEs/SAEs/AESI at the discretion of the site Investigator, in consultation with the Medical Monitor. If the site Investigator deems the event urgent, then study drug should be held and consultation with the Medical Monitor regarding potential restart of study medication at the assigned or a reduced dose should be performed (see Section 6.7)
- Unblinding of subject's study drug treatment assignment (see Section 6.4)
- Subject becomes pregnant or wishes to discontinue birth control measures (see Section 8.4.5)
- Any other reason that, in the opinion of the Investigator, precludes the subject's further participation in the trial

Subjects who permanently discontinue study drug will continue participation in the study, including participation in all remaining visits and assessments until the EoS visit. Subjects who have permanently discontinued study drug will not progress to the OLE study.

Details regarding subjects who discontinue study drug will be recorded on the appropriate page(s) of the eCRF. If a subject discontinues study drug because of an AE, the Investigator may be requested to schedule follow-up visits until the event has resolved or stabilized (Section 4.6).

7.2 Withdrawal of a Subject from the Study

Subjects have the right to withdraw participation in the study at any time and for any reason or for no reason and will be removed from the study upon request. At the time of withdrawal from the study, if possible, an EoS visit should be conducted to complete all assessments scheduled for a safety follow-up visit in either study part as shown in the schedule of assessments (Table 1). Subjects who withdraw prematurely from the study for any reason will not be eligible to participate in the OLE study. These subjects will be followed up as per standard of care. If a subject is unable or unwilling to return to the study center, the reason for withdrawal will be recorded. Each subject's right to withdraw will be honored; subjects who desire no further follow-up contact will be asked to declare so in writing. Details regarding subjects who choose to discontinue study participation will be recorded on the appropriate page(s) of the eCRF.

Reasons for withdrawing, or being withdrawn, from study may include but are not limited to:

- Subject withdraws consent
- Withdrawal from participation due to subject convenience (i.e., due to a change in the subject's willingness or ability to attend study visits, e.g., resulting from a new job, work schedule change, or move to another geographical area)
- Lost to follow-up (i.e., the Investigator has exhausted all reasonable methods of contacting the subject, which should be documented by at least 3 unsuccessful attempts to contact the subject) (Section 7.3)

- Chronic or recurrent subject noncompliance, defined as failure to comply with protocol requirements as determined by the Investigator or the Sponsor.
- Death
- Other

If a subject withdraws consent, Mineralys may retain and continue to use any data collected before such a withdrawal of consent.

7.3 Lost to Follow Up

A subject will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the study.
- The Investigator or designee must make every effort to regain contact with the subject. Three telephone calls, and if necessary, a certified letter should be sent to the subject's last known mailing address or local equivalent methods. These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, the site will continue efforts to contact the subject at each study visit per schedule and document their effort. No subject will be considered a true loss to follow up until the end of the trial.
- At the end of the trial, vital status can be verified by the study site by contacting the subject's primary care physician or other sources according to local rules and regulations.

8. STUDY ASSESSMENTS AND PROCEDURES

Table 1 outlines the schedule of assessments and study conduct details, respectively, for all subjects and all study periods. Protocol waivers or exemptions are not allowed.

- Informed consent must be obtained before any trial related activity. The process of obtaining informed consent must be documented as part of the subject's source documentation.
- At Screening, subjects will be provided with a card stating that they are participating in a trial and giving contact details of relevant trial site staff.
- Adherence to the study design requirements is essential and required for study conduct.
- Any deviation from study conduct, as outlined in the protocol and/or SRM, will be captured and recorded as a protocol deviation.
- Acute safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the subject requires dose modification or discontinuation of study drug.
- All Screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a Screening Log to record details of all subjects screened and to confirm eligibility or record reasons for Screening failure, as applicable.
- Source data of clinical assessments performed and recorded in the eCRF must be available and will usually be the subject's medical records. Additional recordings to be considered source data include, but are not limited to laboratory reports, AOBP, and ECG assessments.
- Assessments should be carried out according to the institution's standard of practice unless otherwise specified in the current section. Efforts should be made to limit the bias between assessments.
- Phone calls may be conducted between study visits to follow up on study drug compliance, and/or as a general follow-up for any questions or clarifications that the subject may have.

8.1 Demographics and Other Baseline Characteristics

8.1.1. Medical History

Medical history data are to be collected at the Screening Visit. For female subjects of childbearing potential, the date of the last menstrual period should be noted. Data will be updated at subsequent visits, as appropriate.

8.1.2. Concomitant Medications

A detailed history of medications and procedures will be documented for each subject at the Screening Visit. Concurrent medications (especially changes in medication) will be documented for each subject at each scheduled visit.

Any medication that in the opinion of the Investigator will interfere with the study drugs is prohibited (see Section 6.9).

8.1.3. Demographic Data

Subject demographic data will be collected at the Screening Visits. These data include the year of birth, age, gender, race, and other relevant baseline characteristics.

8.2 Efficacy Assessments

8.2.1. First Morning Urine Void Measurements

First morning urine void collection will be performed as per the schedule of assessments (Table 1) and outlined in the SRM. Subjects will be given first morning void collection kits to take home. A mid-stream sample of the first morning urine will be collected in the morning when they wake up and prior to dosing with study drug. The date and time of urine collection should be recorded. A detailed description for urine collection and storage will be provided in the laboratory manual and instructions will be provided to the subjects. During Screening, one first morning urine void is to be brought in, in the first week after Screening Visit to determine eligibility. An unscheduled visit during Screening for subjects to return first morning void must take place a minimum of 7 days prior to the Week 0 visit so that the result is available for eligibility review. The sample needs to be 200-5000 mg/g inclusive to meet eligibility criteria. Samples will be assessed for albumin, protein, and creatinine.

8.2.2. 24-hour Urine Measurements

24-hour urine collection will be performed as per the schedule of assessments (Table 1) and outlined in the SRM. Subjects will be provided with a 24-hour urine collection kit to take home for collection of urine preceding the analysis days outlined in the schedule of assessments (Table 1). The 24-hour urine collection starts after the first morning urine and is collected for 24 hours with the last urine added the morning of the second day. The date and time of the start and end of the urine collection should be recorded. 24-hour urine samples will be used to measure 24-hour albumin, protein, sodium, potassium, cortisol, and aldosterone. An aliquot of urine will be retained for future assessments.

8.2.3. Blood Pressure Measurements

Measurement of BP will be done as per the schedules of assessments (**Table 1**) and outlined in the SRM and the AOBP site manual. This is essential to classify individuals and record study treatment effect; consequently, BP should be measured using an automatic BP device at the site provided by the Sponsor that is identical for all participating sites and managed by qualified personnel. Deviations from this must be approved by the Sponsor prior to implementation. Subjects should be seated when performing the AOBP assessment. In addition, the same person should use the BP device for a given subject at each visit whenever possible, and the measurement should be performed using the same arm of the subject and the appropriate cuff size, as determined during the Screening visit.

Details on BP procedure (measurement and transfer of data) including subject preparation (e.g., arm selection, arm position, cuff size) will be provided in the SRM and/or AOBP Site Manual.

Heart rate will also be recorded and collected with all AOBP measurements. Seated and standing SBPs and DBPs will be recorded and collected along with corresponding heart rates. Orthostatic BP change will be calculated and recorded as described in the SRM.

8.2.4. Biomarker Analysis

For the efficacy and safety assessments of the study, biomarkers are measured at a central laboratory to allow estimation of change from baseline. These measurements will be performed as per the schedule of assessments (**Table 1**) and outlined in the SRM.

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8.3 Safety Assessments

8.3.1. Physical Examination

A thorough physical examination will be performed by trained medical personnel at Screening and should include an evaluation of the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems. Height will be measured at Screening only. On other visits, a limited, symptom-directed physical examination should be performed. Changes from baseline abnormalities should be recorded in source documents. New or worsened clinically significant abnormalities should be recorded as AEs on the AE eCRF.

8.3.2. Vital Signs

In addition to BP and heart rate (see Section 8.2.3), body temperature, and respiratory rate will be assessed with the subjects in a seated position. Subjects should be seated for at least 5 min before taking the measurement.

8.3.3. Electrocardiogram

Single 12-lead ECGs will be recorded as per the schedule of assessments (**Table 1**). Clinically significant abnormal ECG findings should be reported as AEs and treated as clinically appropriate. In addition, a 12-lead ECG assessment will be performed on subjects with a re-check serum potassium as outlined in Section 8.4.7.1.

8.3.4. Clinical Safety Laboratory Tests

Blood and urine samples will be collected and clinical safety laboratory tests will be conducted by a central or local laboratory as per the schedule of assessments (**Table 1**). Local labs will be collected as per local guidelines. Instructions for collection, preparation, handling, and shipping of central clinical laboratory specimens are provided in the laboratory manual for the study. Analytes for clinical safety labs are listed in Table 3 (Appendix 12.5).

Subjects will be given a 24-hour urine collection kit to take home for collection of urine as outlined in the schedule of assessments (**Table 1**). Subjects with a morning serum cortisol assessment >35 µg/dL will perform an unscheduled 24-hour urine collection for assessment of 24-hour urinary free cortisol (Section 8.4.7.5).

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8.3.6. Pregnancy Testing

Pregnancy tests are required for women of childbearing potential (WOCBP) only. A serum pregnancy test will be performed at Screening. Urine pregnancy tests will be performed at other visits as per the schedule of assessments (**Table 1**). If urine pregnancy test is positive, a serum pregnancy test will be collected to confirm results at the local laboratory.

8.4 Adverse Events, Serious Adverse Events, and Other Safety Reporting

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE, and remain responsible for following up on all AEs and SAEs (Appendix 12.6).

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

For subjects rolling over into the OLE, all AEs and SAEs will be collected from signing of the study ICF until just before the first assessment in the OLE study. All AESIs will be collected from Randomization until just before the first assessment in the OLE study. For subjects not participating in the OLE, all AEs and SAEs will be collected from signing of the ICF to 28 days post the last dose of study drug. All AESIs will be collected from Randomization until the EOS visit.

Adverse events that begin before the start of study drug (lorundrostat or placebo) at Randomization, but after obtaining informed consent will not be considered TEAEs.

Under no circumstance should the reporting of SAEs and AESI exceed 24 hours (Appendix 12.6.4.1). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after the conclusion of study participation (i.e., after the completion of the EoS visit). However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study drug or study participation, the Investigator must notify the Sponsor promptly.

In the event that study drug is interrupted, AEs and SAEs will be collected throughout the interruption. If study drug is permanently discontinued for any reason, the reason will be recorded and the subject should be encouraged to remain in the study so that important safety information can be obtained. All AEs and SAEs leading to discontinuation of study drug or discontinuation of study will be collected. Once a subject withdraws consent to participate in the study, no further information can be collected from the subject.

8.4.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

Investigators will seek information on AEs at each subject contact. All AEs, whether reported by the subject or noted by study personnel, will be recorded in the source documents and on the AE form of the eCRF.

A consistent, nondirective questioning methodology should be adopted for eliciting AE information at all subject evaluation time points. Examples of nondirective questions include the following:

- "How have you felt since your last study visit?"
- "Have you had any new or changed health problems since you were last here?"

The method of recording, evaluating, and assessing causality of AEs and SAEs, and the procedures for completing and transmitting SAE reports are provided in Appendix 12.6.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All AEs, SAEs, and AESI (as defined in Section 8.4.7) will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3).

8.4.4. Regulatory Reporting Requirements for SAEs

- Prompt notification (within 24 hours) by the Investigator to the Sponsor/designee of an SAE is essential so that regulatory obligations and ethical responsibilities towards the safety of subject and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and Investigators.
- An Investigator who receives an investigational new drug (IND) safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local and institutional requirements.
- IND safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to Investigators.
- Any life-threatening (i.e., imminent risk of death) or fatal AE that occurs while on study drug should be submitted to the Medical Monitor/designee with written case details on a safety event report form within 24 hours

8.4.5. Pregnancy

- Details of all pregnancies in female subjects and female partners of male subjects will be collected from Screening until either just prior to the start of the OLE study, or until 28 days after the last subject visit (for those not participating in the OLE study).
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the female subject or female partner of male subject (after obtaining the necessary signed informed consent from the female partner) pregnancy.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs and will be reported as such.
- The subject/pregnant female partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the subject/pregnant female partner and the neonate and the information will be forwarded to the Sponsor/designee.
- Any post-study pregnancy-related SAE considered reasonably related to the study drug by the Investigator will be reported to the Sponsor (as described in Section 8.4.4 and 12.6.4). While the Investigator is not obligated to actively seek this information in former study subject/pregnant female partner, they may learn of an SAE through spontaneous reporting.

8.4.6. Death Events

Any AE resulting in death that occurs for subjects rolling over into the OLE will be collected from signing of the study ICF until just before the first assessment in the OLE study. For subjects not participating in the OLE, any AE resulting in death will be collected from signing of the ICF up to 28 days after the last dose of the study drug. All AEs resulting in death are considered SAEs and must be reported to the Sponsor (or designee) and/or the study Medical Monitor within 24 hours of awareness of the event.

All deaths that occur during the protocol-specified AE reporting period (Section 8.4.1) regardless of attribution, will be recorded on an eCRF and reported in a safety event report form and expeditiously sent to the Sponsor/designee. This includes death attributed to progression of disease.

When recording a death on an eCRF or safety event report form, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept whenever possible. When reporting SAEs, “death” should not be reported as an SAE term, but rather as the outcome of a specific SAE unless the event preceding the death in unknown. If an autopsy was performed, the autopsy report should be provided.

8.4.7. Adverse Events of Special Interest

Treatment-emergent AESIs are required to be reported by the Investigator to the Sponsor/designee immediately (i.e., no more than 24 hours after learning of the event) regardless of their causality to the study drug treatment. The most appropriate diagnosis should be recorded, or if a diagnosis cannot be established, the abnormal laboratory values should be recorded on the safety event report form and reported to the Sponsor/designee immediately, either as an AESI or and/or a SAE.

NOTE: If any of the following events are reported as SAEs then there is no need to complete a separate AESI form.

The AESI for all study drugs (lorundrostat and placebo) include the following:

- Modification of study drug dose due to hyperkalemia (e.g., dose reduction, dose hold, or permanent dose discontinuation)
- Modification of study drug dose due to hyponatremia (e.g., dose reduction, dose hold, or permanent dose discontinuation)

- Hypotension with symptoms (e.g., light-headedness, dizziness, presyncope, or syncope)
- Severely elevated BP (AOBP SBP [redacted] or AOBP DBP [redacted])
- Modification of study drug dose due to hypercortisolism (morning serum cortisol [redacted], confirmed by 24-hour urinary free cortisol)
- Discontinuation of study drug due to hypocortisolism confirmed by ACTH (Cosyntropin) stimulation test
- Overdose of study drug
- Modification of study drug dose due to reduction in kidney function (e.g., dose reduction, dose hold, or permanent dose discontinuation)

8.4.7.1. Hyperkalemia

All subjects will be regularly monitored for the occurrence of hyperkalemia. This includes baseline Screening and regular intervals as noted in **Table 1**. The Investigator can perform a re-test at any time if they consider it necessary to confirm the serum potassium concentration.

If hyperkalemia is felt to be spurious in the opinion of the PI (such as from hemolysis), then a repeat value should be obtained within 48 hours and the Medical Monitor should be contacted to discuss potentially holding study drug while confirmatory results are pending. Treatment for hyperkalemia, including potassium binders, is allowed. If a new treatment for hyperkalemia is initiated on study, please notify the Medical Montior.

In any instance when an ECG is performed, if the ECG shows new signs consistent with hyperkalemia, refer the subject to an urgent care center or other appropriate care facility for further evaluation and intervention, and consult the Medical Monitor.

- Any subject with serum potassium [redacted] mmol/L will remain on study drug treatment.
- Any subject with a serum potassium [redacted] L but [redacted].0 [redacted]/L will continue study drug [redacted]) performed within 72 h of the initial local lab result.
  - If upon re-check serum potassium [redacted], continue study drug at the same dose.
  - If upon re-check serum potassium is [redacted] L [redacted].0 [redacted] reduce study drug dose and re-check serum potassium at the next study visit (or within 2 weeks, whichever is sooner).
- Any subject with a serum potassium [redacted].0 [redacted] L [redacted].5 [redacted]/L will have study drug held immediately and will have a repeat serum potassium and a 12-lead ECG performed within 24 hours of the initial local laboratory result. Continue to hold study drug until the result of the repeat serum potassium and ECG are assessed.
  - If upon re-check serum potassium is [redacted]5.5 [redacted] restart study drug at same dose and repeat serum potassium at the next scheduled study visit.
  - If upon re-check serum potassium [redacted]5.5 [redacted] L [redacted].0 [redacted] and the ECG is normal, restart the study drug at a reduced dose and re-check serum potassium within 72 hours. If re-check potassium is [redacted] L, follow bullet below.
  - If serum potassium remains [redacted] permanently discontinue study drug, and [redacted] and ECG within 48 hours of the most recent assessment and continue to monitor serum potassium until valu [redacted] Consult with Medical Monitor.

- Any subject with a serum potassium [redacted] will have study drug held immediately and should be referred to urgent care center or other appropriate care facility for further evaluation (including repeat potassium and ECG) and intervention. Continue to hold study drug until the result of the repeat serum potassium and ECG within the emergency setting are known and assessed. Consult with Medical Monitor.
    - If upon re-check serum potassium is ≤5.5 mmol/L, restart study drug at same dose and repeat serum potassium at next scheduled study visit.
    - If upon re-check serum potassium is >5.5 mmol/L but ≤6.0 mmol/L and the ECG is normal, restart study drug at a reduced dose and re-check serum potassium within 72 hours. If re-check potassium is >6.0 mmol/L, follow the bullet below.
    - If serum potassium remains >6.0 mmol/L, permanently discontinue study drug, repeat serum potassium and ECG within 48 hours of the most recent assessment, and continue to monitor serum potassium until value ≤5.1 mmol/L. Consult with Medical Monitor.

8.4.7.2. Hyponatremia

All subjects will be regularly monitored for the occurrence of hyponatremia. This includes baseline Screening and regular intervals as noted in **Table 1**. The Investigator can perform a re-test at any time if they consider it necessary to confirm the serum potassium concentration.

- Any subject with a serum sodium of [redacted] corrected for hyperglycemia) will be asked to return to the clinic for a repeat test (re-check) of their serum sodium at a local laboratory, as follows:
    - If a subject experiences mild hyponatremia, defined as a corrected serum sodium [redacted] and remains asymptomatic, sodium levels should be rechecked within the next 72 – 96 hours. Based on the opinion of the PI (in conjunction with Medical Monitor if needed) study drug may be continued or held until re-checked.
        - If upon re-check, the corrected serum sodium returns to normal [redacted] restart or continue study drug at the same dose prior to event onset.
        - If upon re-check, the corrected serum sodium remains [redacted] the results should be discussed with the Medical Monitor and a decision made if study drug should be continued, held, or dose reduced
    - If a subject experiences moderate or severe hyponatremia, defined as a corrected serum sodium [redacted] study drug should be held and sodium levels should be rechecked within the next 48 hours.
        - If upon re-check, the corrected serum sodium returns to normal [redacted] restart study drug at a lower dose. The Investigator should consult with the Medical Monitor to discuss the underlying etiology of hyponatremia.
        - If upon re-check, the corrected sodium level remains [redacted] continue to hold study drug and retest serum sodium levels at least weekly until values return to normal [redacted].

- If a subject experiences severe hyponatremia, defined as a corrected serum sodium level [redacted], in associations with signs and symptoms (e.g., nausea, vomiting, confusion, headache, loss of energy and fatigue, muscle weakness), the subject should be asked to visit the emergency room for re-check, follow-up, examination and hospitalization (if clinically warranted). The Medical Monitor should be contacted to discuss the appropriateness of ongoing study participation based on etiology, treatment in the emergency room, and repeat sodium levels. If there is no explanation for the occurrence of severe hyponatremia, study drug should be permanently discontinued. If upon re-check, corrected sodium levels return to moderate or mild hyponatremia levels, the actions outlined above should be followed.

8.4.7.3. Symptomatic and Asymptomatic Hypotension

If subjects experience symptoms of hypotension (e.g., light-headedness, dizziness, presyncope, or syncope) during the study, it will be medically managed by the Investigator in communication with the Medical Monitor. Dose reduction of study drug according to the instructions in the SRM may be considered.

In cases of hypotension without symptoms (AOBP DBP [redacted], or DBP between [redacted] <85 mmHg plus AOBP SBP [redacted]), the lorundrostat dose should be reduced first. If a subject experiences symptoms of hypotension (e.g., frequent light headedness, pre-syncope, dizziness) but does not meet the above defined BP threshold for hypotension, the study drug dose should be reduced. Dose reduction of the study drug is the first step. If symptoms and/or BP thresholds persist following dose reduction, the subject may be discontinued from study drug in consultation with the Medical Monitor.

8.4.7.4. Severely Elevated Blood Pressure

Subjects with systolic AOBP of [redacted] or diastolic AOBP of [redacted] will have any prescribed AHT regimen adjusted as described in the SRM. If additional medications are needed, doxazosin 1 mg is recommended, but medication additions are performed at the Investigator's discretion in consultation with the Medical Monitor.

8.4.7.5. Hypercortisolism

All subjects will be monitored for signs and symptoms of hypercortisolism (i.e., new onset or unexplained worsening of: hyperglycemia, hypertension, weight gain, abdominal striae, round facies).

Any subject with serum cortisol [redacted] (morning measurement) will perform an unscheduled 24-hour urine collection for assessment of 24-hour urinary free cortisol. The subject will continue the study drug with no dose adjustment.

- Any subject with a 24-hour urinary free cortisol level [redacted] and [redacted] ill perform a repeat test 4 weeks later.
- Any subject with a 24-hour urinary free cortisol level [redacted] ill have their study drug dose reduced by 50% and will perform a repeat test 4

8.4.7.6. Hypocortisolism

Subjects will have their serum cortisol measured as per the schedule of assessments, with the blood draw performed as close to 8 AM as possible.

- Any subject with a morning serum cortisol [redacted] will undergo an ACTH stimulation test within 1 week of the result being known.
- Any subject with morning serum cortisol [redacted] L accompanied by ≥2 signs and symptoms of adrenal insufficiency (i.e., weakness, loss of appetite, unintentional weight loss, hyponatremia, hypoglycemia) plus clinical findings of orthostatic hypotension, pre-syncope, or syncope, will undergo an ACTH stimulation test within 48 hours of the result being known.
    - If associated with a concurrent acute illness, including COVID-19, the ACTH stimulation test timing will be at the discretion of Investigator but may be delayed for no more than 5 days from the morning serum cortisol result being known.
- Any subject with morning serum cortisol [redacted] L accompanied by [redacted] 2 [redacted] and symptoms of adrenal insufficiency but no BP or laboratory abnormalities, will undergo an ACTH stimulation test within 1 week of the result being known.
- Any subject with morning serum cortisol [redacted] accompanied by asymptomatic orthostatic hypotension with hypoglycemia or hyponatremia will undergo an ACTH stimulation test within 1 week of the result being known.
- Any subject with an ACTH test result diagnostic of adrenal insufficiency will immediately discontinue study drug and will be referred to specialized care (e.g., endocrinologist/urgent care) for further management. The subject is not required to withdraw from the study in such cases.

8.4.7.7. Overdose

For this study, any dose of study drug greater than 200 mg within a 24-hour period will be considered an overdose and will be recorded in the eCRF as an AESI. In the event of an overdose, the Investigator should:

- Contact the Medical Monitor immediately.
- Evaluate the subject to determine, in consultation with the Medical Monitor, whether study drug should be interrupted or whether the subsequent study dose should be reduced.
- Closely monitor the subject for any AEs/SAEs and laboratory abnormalities.

For dapagliflozin, the FDA label states: Contact the Poison Control Center. It is also reasonable to employ supportive measures as dictated by the subject's clinical status. The removal of dapagliflozin by hemodialysis has not been studied.

8.4.8. Safety Monitoring Considerations

A DMC will meet periodically to monitor the study. The primary function of this committee is safety monitoring. As part of these reviews, the DMC will receive summaries of study conduct measures as well as unblinded safety and efficacy data. The DMC may recommend discontinuing enrollment for safety. The full scope and responsibilities of the DMC will be described in the DMC charter per the Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees.

9. STATISTICAL CONSIDERATIONS

This is a randomized, placebo controlled, crossover study with a two-period, two-sequence (2x2) design. Details of the statistical analysis, including the handling of missing values will be described in the statistical analysis plan (SAP). This section provides key elements of the statistical approaches foreseen at the time of planning the study.

9.1 Analysis Sets

The intent-to-treat (ITT) analysis set includes all subjects, regardless of whether treatment was received.

The full analysis set (FAS) will include all subjects who receive at least one dose of study drug. Subjects will be categorized according to the treatment assignment.

The safety analysis set (SAF) will include all subjects who receive at least one dose of study drug. Subjects will be categorized according to the treatment received in the respective study periods.

The population pharmacokinetics (popPK) analysis set will include all subjects who received at least one dose of lorundrostat and had at least one evaluable popPK sample taken. Subjects in this analysis set will be categorized according to the treatment received.

9.2 Statistical Analyses

Unless otherwise specified, demographic and baseline characteristics will be summarized for the ITT analysis set. Efficacy outcomes will be analyzed using the FAS, unless otherwise specified. Safety outcome analyses will be performed on the SAF.

For continuous variables, the descriptive statistics of n, mean, standard deviation, median, 25^{th} percentile, 75^{th} percentile, minimum, and maximum will be summarized. The frequency and percentage of observed levels will be reported for all categorical variables.

The primary analysis of the primary efficacy estimand will assess the superiority of lorundrostat treatment compared to placebo in change from baseline in AOBP SBP at Study Week 4. Each subject contributes two pairs of treatment observations (change at Study Week 4 from Study Week 0 and, change at Study Week 12 from Study Week 8). A mixed model for repeated measures (MMRM) including treatment arm (Lorundrostat and Placebo), sequence (LP and PL) and Treatment Period (Period 1 and Period 2) as fixed effects, subject (sequence), as random (repeated) effect, and baseline (Study Week 0 and Study Week 8) AOBP SBP as a covariate will be used in the analysis. An estimate of the least square means, and the associated standard errors and 90% confidence intervals (CIs) of change from baseline at Study Week 4 will be reported for each arm. The primary analysis will be based on the evaluation of the least square estimate for the treatment arm effect which represents placebo-adjusted effect in lorundrostat treatment periods. Prior to the main estimation, a general linear model with effects of sequence, subject (sequence), period and treatment will be fitted to evaluate the existence of possible carryover/sequence effect.

Statistical approaches for the exploratory and pharmacokinetic endpoints will be described in the SAP.

9.3 Alpha Value

The overall alpha (α) value is set to one-sided 0.05. There will be no adjustment for multiplicity.

9.4 Safety Analyses

AEs will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC), preferred term (PT), as well as by severity, causality, and time to occurrence.

9.5 Sample Size Determination

Approximately 60 subjects randomized in a 1:1 ratio to the two sequences (LP and PL) will provide 85% power to detect a placebo-adjusted change in AOBP SBP of at least 5.5 mmHg, assuming a 14 mmHg as a standard deviation of change, and 1-sided alpha of 0.05.

9.6 Handling of Missing Data

Missing values imputation will be described in SAP.

[redacted]

10. ETHICAL AND ADMINISTRATIVE CONSIDERATIONS

10.1 Compliance Statement

This study will be conducted in accordance with the protocol and with US FDA and the International Council for Harmonisation (ICH) good clinical practice (GCP) guidelines, the Declaration of Helsinki, and any applicable local health authority and IRB/IEC requirements.

To the extent applicable, all references to the FDA, Federal Food, Drug, and Cosmetic Act, Code of Federal Regulations (CFR), ICH, GCP, and the like shall be interpreted as also referring to any corresponding requirements of local regulatory agencies, regulations, and laws. If there is any discrepancy between FDA, ICH, and local requirements, the most stringent standard shall apply.

10.2 Principal Investigator Responsibilities

As required by FDA regulation (21 CFR Part 56) and ICH guidelines for GCP, the Investigator at each study site must obtain IRB/IEC review and approval of the study protocol, ICFs, subject recruitment materials, and any other pertinent documents before any study related activities involving subjects are performed.

As required in 21 CFR Part 50 and ICH guidelines for GCP, the Investigator or designee must comply with the informed consent process and ensure that each subject enrolled in this clinical study understands the information presented in the IRB/IEC approved ICF and agrees voluntarily to participate in the clinical study.

The PI or designee must submit to the IRB/IEC any written safety report or update (e.g., amended IB or safety amendments and updates) provided by the Sponsor or representative, according to the IRB/IEC specific reporting requirements.

The PI must inform the IRB/IEC of the progress of the clinical study and report any non-administrative changes made to the protocol; in any case, the Investigator must provide an update to the IRB at least once a year or in accordance with IRB/IEC continuing approval requirements.

The PI must maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on eCRFs or other reporting forms will be included on a Delegation of Authority form.

The clinical study report will be signed by the PI or, in the case of multicenter studies, the coordinating Investigator. The coordinating Investigator, identified by the Sponsor, will be any or all of the following:

- A recognized expert in the therapeutic area.
- An Investigator who provided significant contributions to either the design or interpretation of the study.
- An Investigator contributing a high number of eligible subjects.

10.3 Institutional Review Board Review

A copy of the protocol, proposed ICF, other written subject information, and any proposed advertising material must be submitted to the IRB/IEC for written approval. A copy of the written approval of the protocol and ICF must be received by the Sponsor before recruitment of subjects into the study and shipment of medicinal products.

The PI must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. The PI is to notify the IRB of deviations from the protocol or SAEs occurring at the site and other AE reports received from the Sponsor, in accordance with local procedures.

The PI is responsible for obtaining annual IRB/IEC approval/renewal as applicable throughout the duration of the study. Copies of the Investigator's reports and the IRB/IEC continuance of approval must be sent to the Sponsor.

10.4 Informed Consent and Human Subject Protection

A study ICF will be provided for the PI to prepare the informed consent documents to be used at their site. Updates to the template are to be communicated formally in writing from the Sponsor's to the Investigator. The written informed consent document is to be prepared in the language(s) of the potential subject population. The ICF should meet regulatory, Sponsor's, institutional, and other applicable requirements, be approved by the IRB/IEC prior to use for consenting prospective subjects and be in the language understandable by the study subject or subject's legally acceptable representative (LAR).

Before a subject's participation in the study, the Investigator will obtain written informed consent from the subject or subject's LAR. A LAR is an individual or entity authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the clinical study. The use of a LAR will be limited to regions where it is allowed by local regulations, and where allowed by protocol.

The subject should not undergo any study-related procedures or assessments before the subject's written informed consent has been obtained.

During the informed consent process, the Investigator/authorized designee will explain to the subject/LAR the nature of the study, including the potential risks and benefits, allow the subject/LAR sufficient time to ask any questions regarding the study, and answer all the questions. The subject/LAR will then sign and personally date the ICF. The authorized person obtaining the informed consent must also sign the ICF. A copy of the ICF must be provided to the subject/LAR. The original signed ICF will be retained in accordance with institutional policy and other applicable requirements, and a copy of the signed ICF will be provided to the subject/LAR. Study subjects must be reconsented to the most current version of the ICF during their participation in the study.

The Investigator/designee will ask the subject/LAR if the subject has a primary care physician and if the subject agrees to have their primary care physician informed of the subject's participation in the clinical study. If the subject/LAR agrees to such notification, the Investigator/designee will inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the Investigator will be acting in that capacity, it will be documented in the subject's medical record/source documents. The acquisition of informed consent and the subject's/LAR's agreement or refusal of their notification of the primary care physician should be documented in the subject's medical records/source documents.

If a potential subject is illiterate or visually impaired and does not have a LAR, an impartial witness should be present during the entire informed consent process to read the ICF to the subject/LAR. Thereafter, both the subject and the witness must sign the ICF to attest that the subject/LAR understood the nature of the study, asked questions and received answers, and the informed consent was freely given.

10.5 Confidentiality

The Investigator must ensure that the subject's confidentiality is maintained for documents submitted to the Sponsor, including the following:

- Subjects are to be identified by a unique subject identification number.
- The date of birth is to be documented in accordance with local laws and regulations.
- On the eCRF demographics page, in addition to the unique subject identification number, the subject's age at time of enrollment is to be included.
- For SAEs reported to the Sponsor, any source documentation provided (e.g., medical records, laboratory results) must have any subject identifier (e.g., subject name, initials, medical records number) fully redacted (i.e., blacked out) prior to transmission.

Documents that are not submitted to the Sponsor (e.g., signed ICFs) are to be kept in confidence by the Investigator, except as described below.

In compliance with the CFR/ ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to their study related records, including personal information.

10.6 Urgent Safety Measures

The Sponsor or Investigator may take appropriate urgent safety measures to protect trial subjects from any immediate hazard to their health or safety. Urgent safety measures may be taken without prior authorization. The trial may continue with the urgent safety measures in place.

The Investigator must inform the Sponsor IMMEDIATELY if the study site initiates an urgent safety measure.

The notification must include all the following:

- Date of the urgent safety measure.
- Who made the decision.
- Why the action was taken.

The Investigator will provide any other information that may be required to enable the Sponsor to report and manage the urgent safety measure in accordance with the current regulatory and ethical requirements for expedited reporting and closeout.

10.7 Study Monitoring

The Sponsor's representative(s) are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (e.g., eCRFs and other pertinent data) provided that subject confidentiality is respected.

The Sponsor's representative(s) are responsible for verifying the eCRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and

adherence to local regulations on the conduct of clinical research. The Sponsor's representative(s) are to have access to subject medical records and other study related records needed to verify the entries on the eCRFs. The Investigator agrees to cooperate with the Sponsor's representative(s) to ensure that any problems detected in the course of these monitoring visits, including delays in completing eCRFs, are resolved.

10.8 Audits and Inspections

As stipulated by 21 CFR §312.58 and ICH guidelines for GCP, a representative of the Sponsor, the FDA, or other regulatory agencies may conduct periodic site audits or inspections. The Investigator or designee will provide these representatives with access to all requested materials, including eCRFs and supporting source documents. In addition, the Investigator or other qualified study site personnel are to be available to answer questions, hold interviews, and provide facility tours, if requested.

10.9 Data Collection and Handling

The Investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol required therapies), as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and procedures, the Investigator may search publicly available records (where permitted) to ascertain survival status. This ensures that the data sets produced as an outcome of the study are as comprehensive as possible.

The Investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. Data collection will involve the use of an electronic data capture system, to which only authorized personnel will have access. The Investigator agrees to maintain accurate eCRFs or paper case report forms and source documentation as part of the case histories. The Sponsor will supply the eCRF, which is to be completed in English.

The Investigator or designee must enter all results collected during the clinical study into eCRFs. Guidelines for completion of eCRFs will be reviewed with study site personnel at the site initiation visits. Investigators are responsible for approval of the entered/corrected data. Detailed instructions may be found in the other study specific documents.

All entries made on the eCRF must be verifiable against source documents. In addition to periodic monitoring occurring within the system by study monitors, programmatic edit checks and data listings will be used to review the data for completeness, logic, and adherence to study protocol. As a result of this monitoring and these checks, queries may be electronically issued to the clinical study sites and electronically resolved by those sites.

All data collected in the context of this study will be stored and evaluated according to regulatory requirements and applicable guidance for electronic records. Also, data will be stored and evaluated in such a way as to assure subject confidentiality in accordance with the legal and regulatory requirements applying to protected health information. Study records (e.g., copies of eCRFs, regulatory documents) will be retained at the study site, along with adequate source documentation. The study file and all source data must be retained for the period dictated by the applicable regulatory requirements or by the Sponsor, whichever period is longer. No records may be destroyed without the written approval from the Sponsor.

10.10Maintenance of Source Documents and Recordkeeping Requirements

As stipulated by 21 CFR §312.57 and ICH E6 GCP Consolidated Guidance Section 8, the Investigator or designee will maintain source documentation for this clinical study that documents the treatment and study course of subjects as described in the study manual. Source documents are original documents, data, and records from which the subject's eCRF data are obtained. These include, but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities.

The Investigator must retain all essential documents for this clinical study until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. However, the Investigator may need to retain these documents for a longer period, if required by the applicable regulatory requirements or by an agreement with the Sponsor. The Sponsor representative will be responsible for informing the Investigator and study site regarding when they no longer need to retain these documents. No records may be destroyed without the written approval from the Sponsor

10.11Long-term Retention of Samples for Additional Future Research

Blood and urine specimens will be collected and stored for additional analyses. These samples will be retained for long-term storage by the Sponsor and described in the ICF.

Any blood sample collected according to the schedule of assessments (**Table 1**) may be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure that analytical methods produce reliable and valid data throughout the course of the study. It may also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure data integrity and control.

If permitted by local law and if informed consent is provided by the subject, the Sponsor may do additional testing on remaining samples (i.e., residual and back up) to investigate and better understand the disease and the dose response and/or prediction of response to the study drug. Results from this analysis are to be documented and maintained but are not necessarily reported as part of this study. Samples may be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the subject's treatment course, the results of these exploratory studies are not placed in the subject's medical record and are not to be made available to the subject, members of the subject's family, the subject's personal physician, or other third parties, except as specified in the ICF.

The subject retains the right to request that the sample material be destroyed by contacting the Investigator. Following the request from the subject, the Investigator is to provide the Sponsor with the required study and subject number so that any remaining blood samples and any other components from the cells can be located and destroyed.

Information collected from samples prior to the request for destruction will be retained by the Sponsor. The Sponsor is the exclusive owner of any data, discoveries, and derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the Investigator, at the end of the storage period or as appropriate (e.g., the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the Sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample.

10.12Publication Policy

The institution and Investigator agree not to publish the results of this study without the prior written consent of the Sponsor. As used herein, the term ‘publish’ shall include oral presentations, written abstracts, written poster presentations, and written manuscripts or reviews, etc.

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12. APPENDICES

12.1 List of Abbreviations and Definition of Terms

The following abbreviations and specialist terms are used in this study protocol.

Abbreviation/Term	Definition
ACEi	Angiotensin-converting enzyme inhibitor
ACTH	Adrenocorticotropic hormone
ADL	Activities of daily living
AEs	Adverse events
AESI	Adverse events of special interest
AHT	Anti-hypertensive treatment
ALT	Alanine aminotransferase
ANCA	Anti-neutrophil cytoplasmic antibody
ANCOVA	Analysis of covariance
AOBP	Automated office blood pressure
ARB	Angiotensin receptor blocker
ASI	Aldosterone synthase inhibitor
AST	Aspartate aminotransferase
AUC	Area under the curve
BP	Blood pressure
BMI	Body mass index
BUN	Blood urea nitrogen
CBC	Complete blood count
CDC	Center for Disease Control and Prevention
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CIs	Confidence intervals
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	Maximum observed plasma concentration
COVID-19	Coronavirus disease 2019
CRIC	Chronic Renal Insufficiency Cohort
CVD	Cardiovascular disease
CYP3A4	Cytochrome P450 3A
CYP11B2	Cytochrome P450 11B2 (aldosterone synthase)
DB	Double blind
DBP	Diastolic blood pressure
DMC	Data monitoring committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
ENaC	Epithelial sodium channel
EoS	End of study

Abbreviation/Term	Definition
EOT	End of treatment
ESRD	End stage renal disease
EW	Early withdrawal
FAS	Full analysis set
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good clinical practice
GLP1-RA	Glucagon-like peptide-1 receptor agonist
HbA1c	Glycosylated hemoglobin
HBr	Monohydrobromide
HRT	Hormonal replacement therapy
hsCRP	High-sensitivity C-reactive protein
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IND	Investigational new drug
IRB	Institutional review board
ITT	Intent-to-treat
KIM-1	Kidney injury molecule-1
LAR	Legally acceptable representative
LDH	Lactate dehydrogenase
LP	Lorundrostat-placebo
MAD	Multiple ascending dose
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
MLS-101 (lorundrostat)	A selective aldosterone synthase inhibitor
MMRM	Mixed model for repeated measurements
MR	Mineralocorticoid receptor
MRA	Mineralocorticoid receptor antagonist
NGAL	Neutrophil gelatinase-associated lipocalin
NSAIDs	Nonsteroidal anti-inflammatory agents
NTproBNP	N-terminal (NT)-pro hormone BNP
NYHA	New York Heart Association
OLE	Open label extension
PI	Principal Investigator
PK	Pharmacokinetic
popPK	Population pharmacokinetics
PL	Placebo-lorundrostat
PPIs	Proton pump inhibitors
PRA	Plasma renin activity

Abbreviation/Term	Definition
PT	Preferred term
QD	Once daily
RAAS	Renin-angiotensin-aldosterone system
RBC	Red blood cell
RH	Resistant hypertension
RTSM	Randomization and trial supply management
SAD	Single ascending dose
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SGLT2i	Sodium-glucose cotransporter 2 inhibitor
SOC	System organ class
SRM	Study reference manual
T2DM	Type 2 diabetes mellitus
TEAE	Treatment-emergent adverse event
UACR	Urinary albumin to creatinine ratio
ULN	Upper limit of normal
UNS	Unscheduled visit
US	United States
WBC	White blood cells
WOCBP	Women of childbearing potential

12.2 Investigator's Agreement

Study Number: MLS-101-206

Study Title: A Randomized, Crossover, Double Blind, Placebo Controlled, Phase 2 Study to Evaluate the Efficacy and Safety of Lorundrostat in Addition to Sodium-Glucose Cotransporter-2 Inhibitor, in adults with Hypertension and Chronic Kidney Disease with Albuminuria

Protocol Version: 4.0

Protocol Version Date: 28 March 2024

I have read the protocol and agree to conduct the study in accordance with the protocol and all applicable laws, regulations and guidelines, including, but not limited to, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the United States Code of Federal Regulations, the ethical principles that have their origins in the Declaration of Helsinki, and applicable privacy laws.

The study will not commence without the prior written approval of a properly constituted institutional review board (IRB)/independent ethics committee (IEC). No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB/IEC, except where necessary to eliminate an immediate hazard to subjects.

I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Signature	Date

Printed Name of Principal Investigator

12.3 Sponsor's Signature

Study Number: MLS-101-206

Study Title: A Randomized, Crossover, Double Blind, Placebo Controlled, Phase 2 Study to Evaluate the Efficacy and Safety of Lorundrostat in Addition to Sodium-Glucose Cotransporter-2 Inhibitor, in adults with Hypertension and Chronic Kidney Disease with Albuminuria

Protocol Version: 4.0

Protocol Version Date: 28 March 2024

The protocol has been reviewed and approved by me and is acceptable in its present form.

Signature	Date

Reviewed & Approved By:

David Rodman, MD
Chief Medical Officer

12.4 Contraceptive and Barrier Guidance

12.4.1. Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

1. Premenarchal.

2. Premenopausal female with 1 of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the subject's medical records, medical examination, or medical history interview.

3. Postmenopausal female:

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

12.4.2. Contraception Guidance

Investigators should counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise these subjects on the use of adequate methods of contraception and will check for adherence during study visits. Subjects must agree to use adequate contraception during the study and for 28 days after the last dose of study drug.

Methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - Oral
    - Intravaginal
    - Transdermal

- Progestogen-only hormonal contraception associated with inhibition of ovulation:
    - Oral
    - Injectable
    - Implantable[1]
- Intrauterine device[1]
- Intrauterine hormone-releasing system[1]
- Bilateral tubal occlusion[1]
- Vasectomized partner[1,2]
- Sexual abstinence[3]

Acceptable birth control methods which may not be considered as highly effective – those that result in a failure rate of more than 1% per year – include:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide[4]
- Cap, diaphragm or sponge with spermicide[4]

[1] Contraception methods that are considered to have low user dependency.

[2] Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.

[3] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments.

[4] A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods

12.5 Clinical Laboratory Tests

Clinical safety laboratory tests (Table 3: Clinical Laboratory AnalytesTable 3) will be conducted by a central or local laboratory according to methods and time points specified in the schedule of assessments (**Table 1**). Analytes for clinical safety laboratory tests are listed in Table 3: Clinical Laboratory AnalytesTable 3. The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents. All laboratory tests with values considered clinically significantly abnormal during participation in the study or after the last dose of study drug should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor. If clinically significant values do not return to normal/baseline within a period judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.

Table 3: Clinical Laboratory Analytes

Chemistry	Urine	Other Laboratory Measurements
Sodium Potassium (local lab) Chloride Bicarbonate Magnesium Phosphate Total protein Albumin Calcium Glucose BUN Creatinine eGFR CKD-EPI w/o race Total bilirubin Direct bilirubin AST ALT Alkaline phosphatase Serum aldosterone PRA Serum cortisol Cystatin-C	**First Morning Urine Void:** Creatinine Albumin Protein **Urinalysis, spot urine (central lab):** RBCs Glucose Protein Urine pH Ketones Bilirubin Urine specific gravity Blood **24-hour urine*:** Albumin Protein Free cortisol Aldosterone Sodium Potassium Creatinine	**Hematology - CBC auto differential panel (central lab):** Hematocrit Hemoglobin RBC count WBC count Platelet count MCH MCHC MCV Mean platelet volume Red cell distribution width CBC, nucleated red blood cell WBC differential (basophils, eosinophils, immature granulocytes, lymphocytes, monocytes, neutrophils [%, absolute count]) **Pregnancy Testing:** Serum or Urine Pregnancy (for WOCBP only) FSH (postmenopausal women only) **Biomarkers** (central lab):** hsCRP NTproBNP NGAL KIM-1 Exploratory biomarkers **Other:** HbA_{1c} ACTH Stimulation testing

Refer to the Schedule of Assessments (**Table 1**) for collection time points. * An aliquot of urine will be retained for future assessments. **A serum aliquot, a sample of whole blood for proteomic and genomic assessments, and a mid-stream urine sample will be collected and retained for future biomarker analyses.

Abbreviations: ACTH, adrenocorticotropic hormone; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CBC, complete blood count; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; FSH, follicle-stimulating hormone; HbA_{1c}, glycosylated hemoglobin; hsCRP, high-sensitivity C-reactive protein; KIM-1, kidney injury molecule-1; MCH, Mean corpuscular hemoglobin; MCHC, Mean corpuscular hemoglobin concentration; MCV, Mean corpuscular volume; NGAL, Neutrophil gelatinase-associated lipocalin; NTproBNP, N-terminal (NT)-pro hormone BNP; PRA, plasma renin activity; RBCs, red blood cells; WBC, White blood cell; w/o, without.

12.6 Definitions and Procedures for AEs and SAEs

12.6.1. Definition of AE

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study drug or other protocol-imposed intervention, whether or not considered related to the study drug. Any medical condition or clinically significant laboratory abnormality with an onset before the first dose of study drug is considered a pre-existing condition that will be captured as part of the subject's medical history and will not be considered an AE unless the condition worsens in intensity or frequency after study enrollment.

Events meeting the AE definition include the following:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events not meeting the AE definition include the following:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): The condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.6.2. Definition of SAE

An SAE is any untoward medical occurrence that, at any dose, meets 1 or more of the following criteria:

- Is fatal (i.e., the AE actually causes or leads to death).
- Is life-threatening (i.e., the AE, in the view of the Investigator, places the subject at immediate risk of death at the time of the event; it does not refer to an event which might hypothetically have caused death if more severe).
- Requires or prolongs inpatient hospitalization.
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product(s).
- Is considered a significant medical event by the Investigator (i.e., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

All AEs that do not meet any of the criteria for serious should be regarded as nonserious AEs. Elective hospitalizations for conditions that existed before administration of the study drug are not to be considered SAEs. However, pre-study conditions that worsen during the study and meet the SAE criteria above would be considered SAEs.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (as in mild, moderate, or severe pain); the event itself may be of relatively minor medical significance (such as severe headache). "Serious" is a regulatory definition and is based on subject or event outcome or action criteria usually associated with events that pose a threat to a subject's life or vital functions. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations.

Severity and seriousness should be independently assessed when recording AEs and SAEs.

12.6.3. Recording and Follow-Up of AE and/or SAE

12.6.3.1. Recording of AEs and SAEs

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information.
- It is not acceptable for the Investigator to send photocopies of the subject's medical records to the Sponsor in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all subject identifiers, except for the subject number, will be redacted on the copies of the medical records before submission to the Sponsor.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

12.6.3.2. Assessment of Intensity

The Investigator will assess intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- **Mild**: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Moderate**: Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- **Severe**: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL. Self-care ADL refers to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.

12.6.3.3. Assessment of Causality

The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship. The guideline below should be used to consider relatedness:

"Unlikely" or "Not Related" = there is not a reasonable possibility that the event may have been caused by study drug. The AE:

- May be judged to be due to extraneous causes such as disease or environment or toxic factors
- May be judged to be due to the subject's clinical state or other therapy being administered
- Is not biologically plausible
- Does not reappear or worsen when the study drug is readministered
- Does not follow a temporal sequence from administration of study drug

"Possibly" or "Definitely" = there is a reasonable possibility that the AE may have been caused by the study drug. The AE:

- Follows a temporal sequence from administration of study drug
- Is a known response to the study drug based on clinical or nonclinical data
- Could not be explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other therapy administered
- Disappears or decreases upon cessation or reduction of the study drug
- Reappears or worsens when the study drug is readministered

A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated. The Investigator will also consult the IB and/or product information, for marketed products, in their assessment.

For each AE/SAE, the Investigator must document in the medical notes that they have reviewed the AE/SAE and has provided an assessment of causality. There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the Investigator always assesses causality for every event before the initial transmission of the SAE data to the Sponsor.

The Investigator may change their opinion of causality considering follow-up information and send an SAE follow-up report with the updated causality assessment. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

12.6.3.4. Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to the Sponsor/designee within 24 hours of receipt of the information.

12.6.4. Reporting of SAEs

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up on all AEs and SAEs.

12.6.4.1. SAE Reporting via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the Sponsor or designee will be electronic data capture (EDC).
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information to the Medical Monitor.
- Contacts for SAE reporting will be provided in the SRM.

In the event EDC is unavailable, the paper SAE Report Form and/or the Pregnancy Report Form, as applicable, must be filled out by the Investigator and sent via email within 24 hours of awareness of the event.

12.7 Summary of Changes – Amendment 3

Please refer to the Summary of Changes for Protocol V4.0 for a detailed list of changes and associated rationale.